DEXMEDITOMIDINE VERSUS CLONIDINE AS AN ADJUVANT TO 0.75% ROPIVACAINE FOR EPIDURAL ANAESTHESIA IN LOWER ABDOMINAL AND LOWER LIMB SURGERIES IN A TERTIARY CARE CENTRE - A COMPARATIVE STUDY

Dissertation

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In partial fulfilment of the requirements for

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M.D. ANAESTHESIOLOGY

Branch X

MAY 2018

CERTIFICATE

This is to certify that this dissertation entitled "**Dexmeditomidine versus Clonidine as an Adjuvant to 0.75% Ropivacaine for Epidural Anaesthesia in Lower Abdominal and Lower Limb Surgeries in a Tertiary Care Centre - A Comparative Study"** is a bonafide record of the work done by **Dr. Sathesh Kumar B M,** under guidance and supervision in the Department of Anaesthesiology during the period of her postgraduate study for **M.D Anaesthesiology [Branch-X]** from 2015-2018.

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CERTIFICATE II

This is to certify that this dissertation work titled "**Dexmeditomidine versus Clonidine as an Adjuvant to 0.75% Ropivacaine for Epidural Anaesthesia in Lower Abdominal and Lower Limb Surgeries in a Tertiary Care Centre - A Comparative Study"** of the candidate **Dr. Sathesh Kumar B M,** with registration Number 201520552 for the award of **DOCTOR OF MEDICINE** in the branch of Anaesthesiology [Branch-X]. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 6 percentage of plagiarism in the dissertation.

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DECLARATION

In the following pages is presented a consolidated report of the study on "**Dexmeditomidine versus Clonidine as an Adjuvant to 0.75% Ropivacaine for Epidural Anaesthesia in Lower Abdominal and Lower Limb Surgeries in a Tertiary Care Centre - A Comparative Study"** cases studied and followed up by me at Sree Mookambika Institute of Medical Sciences, Kulasekharam from 2016-2017. This thesis is submitted to the Dr. M.G.R. Medical University, Chennai in partial fulfilment of the rules and regulations for the award of MD Degree examination in Anaesthesiology.

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LIST OF ABBREVATIONS USED

α – Alpha

mcg – Microgram

kg – Kilogram

mg – Milligram

ml – Millimeter

ASA – American Society of Anesthesiology

min – Minutes

L2-L3-L4 – Lumbar

C1 – Cervical

T1 – Thoracic

S1 – Sacral

PCA pumps – Patient Controlled Analgesia Pump

SpO2 – Partial Pressure of Saturation

ADRS – Adverse Drug Reactions

MAP – Mean Arterial Pressure

RL – Ringer Lactate

HR – Heart Rate

COPD – Chronic Obstructive Lung Disease

IV – Intravenous

ABSTRACT

Background:

The quality and duration of analgesia is improved when a local anaesthetics is combined with an alpha 2 adrenergic agonists. Both Clonidine and Dexmedetomidine are alpha 2 adrenergic agonists which have analgesic properties have been extensively studied and it has been established that Clonidine as an adjuvant, effectively prolongs the duration of action of local anaesthetics when given epidurally. There are limited studies demonstrating the effects of epidural Dexmedetomidine and its effects of local anaesthetics.

Aims and objectives:

The aim of this study was to compare the effect of Clonidine and Dexmedetomidine in terms of anaesthesia, analgesia, sedation and side effects when used as an adjuvant to epidural Ropivacaine in lower abdominal and lower limb surgeries.

Methodology:

Patients were randomized to two groups RC and RD by computer generated numbers. Group RC received 15 ml of 0.75% of Ropivacaine with 1mcg/kg Clonidine and group RD 15ml of 0.75% of Ropivacaine with 1 mcg/kg Dexmedetomidine epidurally. Onset of sensory analgesia –using pin prick, onset of motor blockade –using Bromage score, time to 2 dermatome

regression of sensory level , time to first demand for analgesia, sedation – using Ramsay sedation scale, intra operative hemodynamic parameters and complications if any- nausea, vomiting, bradycardia, hypotension were noted.

Results:

Both groups were comparable demographically with respect to age and sex distribution, height and weight characteristics. The onset and duration of sensory blockade was found to be significantly shorter in the RD group ($p<0.005$). The sedation in group RD was found to be significantly better than group RC ($p<0.005$). There was no significant difference found between the two groups in terms of onset of motor blockade and hemodynamic changes. Both groups had a similar incidence of hypotension and bradycardia which was not found to be significant. The side effects in both groups were minimal and comparable between the two groups.

Conclusion:

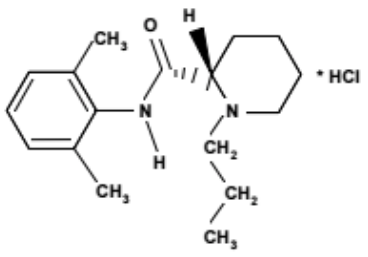
We conclude that the addition of 1mcg/kg Dexmedetomidine as an adjuvant to 0.75% Ropivacaine in epidural anesthesia causes an early onset and prolonged duration of sensory analgesia in comparison to 1mcg/kg Clonidine. Epidural Dexmedetomidine cause better sedation as compared to Clonidine.

Introduction

INTRODUCTION

Epidural anaesthesia is a versatile technique used for providing both anaesthesia and analgesia in the post operative period. It may be combined with regional anaesthesia or other forms of general anaesthesia. It can provide intra operative hemodynamic stability and has been proven to reduce perioperative stress response thus causing a decrease in the complications and help in improving patient outcome. It also helps in early mobilization of the patient by providing relief to post operative pain and decreases the incidence of thromboembolic events.[1-5]

Epidural anaesthesia using Bupivacaine has been researched about in detail in the past. In the recent years Ropivacaine is being used increasingly due to similar analgesic properties but with lesser motor blockade and cardio toxicity. A slightly larger dose of Ropivacaine is required when compared to Bupivacaine but the addition of an adjuvant helps in reducing the total dose required for local anaesthesia and adjuvant also enhances the efficacy, thereby increasing the duration of action and the intensity of blockade.[6-8]



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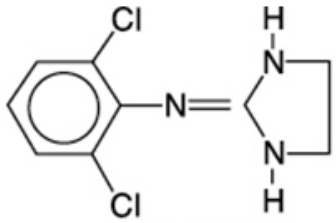
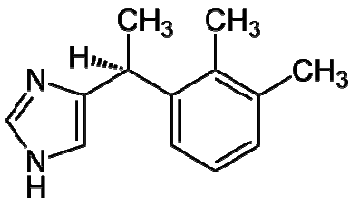
A number of agents such as opioids, ketamine, and alpha agonists can be used as adjuvants to local anaesthetics that act synergistically thereby increasing the efficacy of the local anaesthetic drugs, decreasing the total required dose and toxic side effects of both groups of drugs.[9,10]

The duration and the quality of analgesia can be improved when a local anaesthetic is combined with an alpha 2 adrenergic agonist as adjuvant. Both Dexmedetomidine and Clonidine are alpha 2 adrenergic agonists potentiates local anaesthetic effects and have analgesic properties.[10-12]



(Clonidine)

Clonidine is an alpha 2 adrenergic agonist that enhances the action of local anaesthetic drugs on administration via the epidural or intrathecal route. It acts by blocking the A and C fibres and it causes local vasoconstriction thereby decreasing the intensity and duration of analgesia. It is known to cause sedation and the side effects of its use are bradycardia and hypotension.[13-16]



Dexmedetomidine is a newer alpha 2 adrenergic agonist and is about 8 times more selective α2 adrenoreceptor agonist than Clonidine and hence allows the use of higher drug dosage with less alpha1 effect. It has been found to have hemodynamic stability, anxiolytic, analgesic, sedative, neuroprotective and anaesthetic sparing effect. It causes intense motor blockade and co-operative sedation without increasing the incidence of the adverse effects.[7-19]

Clonidine and Dexmedetomidine act on both pre and post synaptic sympathetic nerve terminals and also has central action which causes a decrease in the sympathetic outflow, leading to its analgesic, sedative, and hemodynamic effects.[13,15,16,18] The effects of Clonidine as an adjuvant with local anaesthetics has been studied extensively and it effectively prolongs the duration of action of the local anaesthetics when given epidurally.

The aim of our study was to compare the effect of Clonidine versus Dexmedetomidine when given as an adjuvant to Ropivacaine in epidural anaesthesia for lower abdominal and lower limb surgeries.

Aims & Objectives

AIMS AND OBJECTIVES

To study and compare the effect of Dexmedetomidine and Clonidine in epidural anaesthesia when given as an adjuvant to 0.75% Ropivacaine

1. The onset and duration of sensory blockade.
2. The onset of motor blockade.
3. The change in intra operative hemodynamic parameters.
4. The level of sedation.
5. Adverse effects (if any)

Hypothesis & Scientific Justification

HYPOTHESIS AND SCIENTIFIC JUSTIFICATION

Hypothesis

Epidural Dexmedetomidine prolongs the duration of anaesthesia with hemodynamic stability and improve post-operative analgesia.

Scientific Justification

Neuraxial block for lower abdominal surgeries are becoming popular as its advantages are many as compared to general anaesthesia. Epidural anaesthesia consists of the interruption of nerve transmission temporarily in the epidural space, an effect produced by the injection of a local anaesthetic (Ropivacaine 15ml) solution in the epidural space. The role of an anesthesiologist is to render pain free surgical procedures.

Anxiety is a common presentation in patients in the perioperative period, that starts few days prior to surgery and reaches its peak just before the induction of anaesthesia. Anxiety is also an intra-operative problem especially in patients undergoing surgical procedures under regional anaesthesia which leads to various manifestations like increasing oxygen demand, respiratory rate and heart rate due to the circulating level of endogenous catecholamines and their effects. Control of the anxiety and pain relief is necessary in an attempt to control the above mentioned metabolic derangements and for the comfort and safety of the patient in the perioperative period.

Dexmedetomidine is a highly selective, potent α_2 - adrenoreceptor agonist that acts centrally with a short duration of action. It has the capability to sedate, hypnotize and provide analgesia that prolongs the duration of sensory and motor blockage obtained with epidural anaesthesia while still maintaining patient arousability and respiratory function. It is used epidurally with Ropivacaine.

In this dissertation we are studying the effects of Dexmedetomidine and Clonidine as an adjuvant to 0.75% Ropivacaine in epidural anaesthesia for lower abdominal or lower limb surgeries.

Review of Literature

REVIEW OF LITERATURE

Role of epidural anaesthesia:

Moraca et al[5] reviewed a number of meta analysis, retrospective and prospective studies to assess the benefits and complications of epidural anaesthesia and analgesia. They concluded that benefits of epidural anaesthesia includes suppression of surgical stress by sympatholysis, stable hemodynamics, reduction in postoperative pulmonary complications and effective pain relief, thus improving patient cooperation for physiotherapy and early mobilization leading to permitting earlier extubation, and reducing the length of stay. They also found 30% reduction of cardiac morbidity, 40% reductions in pulmonary complications and 30% reduction in blood loss. This review indicated significant reduction in perioperative complications and postoperative morbidity were associated with the use of epidural anaesthesia and postoperative analgesia. They also found that adding opioids to local anaesthetics provided better analgesia with less toxicity than either of the drugs alone.

Young et al[2] conducted study on 1,021 patients who required anesthesia for intra abdominal surgeries. The patients were divided into two groups, one receiving intravenous analgesics and other epidural. The patients were monitored for perioperative complications and for 30 days after surgery. Post operative pain, time of ambulation and length of hospital stay was also noted.

Significantly fewer complications were seen with epidural anesthesia and hence concluded that epidural anesthesia and analgesia eliminate the perioperative physiological stress responses. This lead to decrease in surgical complications by providing better analgesia, decreased ICU stay and improving outcomes.

John Riggs et al[4] studied 915 high risk patients undergoing major abdominal surgery in their MASTER anaesthesia Trial Study. They found no significant advantage in combining epidural with general anaesthesia. However there was improvement in analgesia, reduction in respiratory complications and the lower risk of adverse consequences that suggests high-risk patients undergoing major intra abdominal surgery may substantially benefit from effect of combined general and epidural anaesthesia intra operatively and continued postoperative epidural analgesia.

Ropivacaine in epidural anaesthesia:

Sara et al[20] conducted a study in sixty-one patients who were randomly assigned to two groups receiving either 15ml of 0.75% Ropivacaine or 0.5% Bupivacaine epidurally. They looked into the motor and sensory block intensity which was superior with Bupivacaine in the first 30minutes. Later there was no significant difference between the two groups. The duration of sensory and motor block was similar in the two groups and no statistical significant side effects were noted in both group. They concluded that 0.75% Ropivacaine was equipotent to 0.5% Bupivacaine.

Shalina[6] et al compared 0.75% Ropivacaine and 0.5% Bupivacaine in epidural anaesthesia in patients undergoing lower limb orthopaedic surgeries. The patients were randomized into groups to receive Ropivacaine 0.75% and Bupivacaine 0.5%. Epidural block was performed using an 18G Touhys needle and test dose of 2% Lignocaine with 1:200000 Adrenaline was given as test dose after which 20ml of the test solution was injected into the epidural space. The onset of sensory and motor block time to two dermatome regression, duration of analgesia and time to complete motor blockade and side effects were studied. They found that the block parameters were comparable and showed no significant difference.

Clonidine as an adjuvant to local anaesthetics:

Eisenach et al[13] studied the effects of epidural Clonidine in terms of hemodynamic changes and analgesia. All nine patients received a dose of 700mcg of Clonidine in 7ml of isotonic saline which was injected into the epidural catheter over five minutes. The CSF, arterial and venous blood samples were collected to assess the pharmacokinetics along with continuous monitoring of the heart rate and blood pressure. It was found that Clonidine was absorbed rapidly into the systemic circulation after epidural injection with a peak at 11.8±1.9 minutes and it reached peak CSF concentration in about 30 minutes. They inferred that hemodynamic effects correlated to the onset and peak concentrations of Clonidine in the CSF; hence the changes in the heart rate and the blood pressure begin 30 minutes of administration and

peak within 1 to 2 hours and last for 6 to 8 hours. The direct action of Clonidine on the spinal cord causes inhibition of the pre ganglionic nerve fibres causing decrease in the sympathetic outflow resulting in hypotension. Clonidine causes bradycardia by increasing vagal activity and baroreceptor reflexes and also by direct action on the heart. These side effects are dose dependent and are observed at doses above 150 mcg. Sedation after epidural administration is due to systemic absorption and redistribution to the higher centers. Clonidine causes inhibition of the locus coeruleus which is the center of regulation of sleep and wakefulness. It is known to cause dose dependent sedation with an onset of around 20 minutes.

A study was conducted by Bapista et al[21] in 80 patients undergoing hemorrhoidectomy under epidural anaesthesia to assess the safety, pain intensity correlated with age and body mass index, epidural anaesthesia with Ropivacaine and Clonidine, one group received 14ml of Ropivacaine 0.75% alone and the other 14ml of Ropivacaine 0.75% with Clonidine 4mcg/kg. VAS score (p=0.0000) was significantly lower in the Clonidine group. They concluded that Ropivacaine 0.75% along with Clonidine(4mcg/kg) provided better analagesia with fewer hemodynamic changes.

Bajwa et al[22] studied epidural Ropivacaine and Ropivacaine with Clonidine for elective caesarean sections. Patients were randomly divided into two groups with epidural anaesthesia 20ml 0.75% Ropivacaine (group R) and 20ml 0.75% Ropivacaine with 75mcg Clonidine (group RC). Anaesthetic level

achieved was a minimum of T6-T7 dermatome. The onset of analgesia was much shorter in RC group (8.64±2.56 minutes) along with prolonged duration of analgesia (173.50±32.44). Analysis of results revealed that the incidence of bradycardia and hypotension was significantly higher in the Clonidine group ($p>0.05$). The dose requirement for postoperative pain relief was significantly lesser in the RC group. The authors concluded that addition of 75mcg of Clonidine to isobaric Ropivacaine resulted in longer and more effective analgesia.

Alves et al[23] conducted a double blinded study in 70 patients who were undergoing lower abdominal, perineum or lower limb surgeries. The study candidates were divided into 2 groups. In the one group, 0.75% Ropivacaine(150mg) was used and in other, Clonidine(300mcg) and 0.75% Ropivacaine (150mg) was given as epidural anaesthesia. Onset of sensory block at T10 was 18±9 and 17±07 minutes in the control group respectively. But, an increase in the duration of motor and sensory block along with more sedation in the Clonidine group was noticed which was statistically significant ($p<0.001$). Significant bradycardia was seen in the Clonidine group. There was also decreased incidence of tremors.

Clonidine hydrochloride combined with a diuretic agent was given to 57 patients for a period of 6 months to 2 years. It was shown to be an effective agent for the long-term treatment of hypertension. It acts by central inhibition of adrenergic vasomotor stimulation; its withdrawal can cause transient

sympathoadrenal hyperactivity. Dry mouth, constipation and transitory drowsiness were the most common side effects. They diminished with time, even when the dose was progressively increased. Bradycardia was produced by inhibition of cardiac sympathetic innervation, but no serious dysrhythmias occurred.

The drug can be used to advantage as a replacement for Guanethidine or Methyldopa but must be given with a diuretic agent. Orthostatic hypotension was rare. Addition of hydralazine or reserpine in conventional dosage decreased blood pressure very moderately. No change was observed when alpha Methyldopa was added. On the contrary, administration of Clonidine to a patient exhibiting partial adrenergic blockade with Guanethidine augmented the effects of such blockade, causing a further decline in both standing and recumbent blood pressure.

This 3 year of study shows that Clonidine is safe and free from toxicity. It is effective if patiently administered in increasing dosage until proper control of blood pressure is achieved. To evaluate the characteristics of patients receiving Clonidine and its effect on Blood Pressure (BP).Design and method: Retrospective study of patients with chronic kidney disease (CKD) evaluated in Clinic Consultation of Nephrology / Nephrology Hypertension, with uncontrolled hypertension who were treated with Clonidine. In patients with chronic kidney disease hypertension is prevalent and often is very difficult to control, not only due to the severity of the disease itself but also

due to the necessary personalization of prescribed drugs. Central acting alpha agonists are useful as "adjuvant" therapeutic drugs increasing the proportion of patients with controlled disease.

Nakayama M, et al. in 2001 studied analgesic effect of epidural Neostigmine after abdominal hysterectomy. They administered epidural Bupivacaine (10mg) with either saline (control group), 5mcg/kg(5mcg group) or 10 mcg/kg Neostigmine (10mcg group). They concluded that epidural Neostigmine of 10mcg/kg in Bupivacaine provides longer duration of analgesia than does Bupivacaine alone with 5mcg/kg of Neostigmine after Neostigmine.

Shoji K, Saito H and Masaki E in 2004 conducted a study to determine whether pre incisional epidural Neostigmine co administered with Ropivacaine modulates stress response and postoperative pain status. In 20 patients for abdominal hysterectomy either 10ml of 0.75% Ropivacaine alone or along with 300mcg Neostigmine was administered before induction of general anesthesia. They concluded that epidural Neostigmine coadministered with Ropivacaine does not change stress responses and fails to improve the postoperative analgesic effects of the local anesthetic.

Asida SM, Magid MA, Korany A in 2007 conducted a study on sixty patients 1-5years of age admitted for lower abdominal and lower extremity operations and divided into two groups receiving 0.5ml/kg of 0.2%

Ropivacaine and 0.5ml/kg of 0.2% Ropivacaine plus 2mcg/kg Neostigmine to Ropivacaine given by the caudal route to children improves the quality of anaesthesia and postoperative analgesia more than Ropivacaine alone.

Dexmedetomidine as an adjuvant to local anaesthetics:

Paula et al[24] studied the effects of epidural Ropivacaine with Dexmedetomidine in 40 patients undergoing inguinal hernia or varicose vein surgical repair. The patients were divided into 2 groups, the first received 20ml of 0.75% Ropivacaine with 1mcg Dexmedetomidine in the epidural space. The monitored parameters were onset of sensory blockade, time to block dermatomes T12,T10 and T8, maximum dermatome level reached, degree of motor blockade, motor blockade duration, duration of analgesia, need for additional analgesia and sedation. Any occurrence of hypotension and bradycardia and other side effects were also assessed. There was no statistical difference between the two groups in relation to age, weight, height and sex. They found no statistical difference between the two groups in the time taken to block dermatomes T12, T10 and T8. The maximum level of sensory analgesia achieved in both groups was at T6. In the group receiving Dexmedetomidine the duration of sensory blockade, the duration and intensity of motor blockade was found to be significantly higher. It was found that 70% of patients from the group who were given only Ropivacaine injection, required additional sedation. This was in contrast to 26% of patients who received adjuvant Dexmedetomidine. Based on their observations, they

concluded that Dexmedetomidine acts synergistically with 0.75% Ropivacaine as an effective and a safe epidural anesthetic and analgesic.

Yu-Nan Lin et al[25] studied the effects of adding Dexmedetomidine to Ropivacaine for cervical plexus block. Forty patients who underwent thyroid surgery were divided into two groups randomly. Patients in Dexmedetomidine group received 30ml of 0.375% Ropivacaine with 1mcg/mg of Dexmedetomidine while, those in the control group received 30ml of 0.375% Ropivacaine with saline. Onset of sensory blockade was 4.72 minutes in group D and was 6.64 minutes in group C, which was statistically significant. There was also a significant increase in the duration of blockade in group D in comparison to group C. The degree of sedation was also higher in the group D patients. The mean arterial pressure and heart rate in group D was found to be significantly lower than in group C in the dexmedetominidine, two patients were found to have bradycardia and were treated with atropine. Based on these findings, they inferred that the addition Dexmedetomidine to Ropivcaine for cervical plexus block could shorten the onset and extend the duration of analgesia, while providing adequate sedation.

Oriol-Lopez et al[26] conducted a study in 40 patients between the ages of 18 to 65 years who underwent lower abdominal or lower limb surgery under epidural anesthesia. 2% Lignocaine with adrenaline was given along with 1mcg/kg Dexmedetomidine was administrated through the epidural needle. The patient was then assessed for sedation using Ramsays sedation

scale and hemodynamic changes, degree of analgesia were assessed and recorded at 5, 10, 15 and 30 minutes, subsequently every half hour until the end of the anesthetic and surgical events. 17% of the patients had a sedation score of 3 within 5 minutes and 90% of the patients had a sedation level of 3-4 from 15 to 90 minutes, 4 patients had a sedation score of 5 from 30-60 minutes. They concluded that adequate sedation was maintained between 10 to 120 minutes with a single epidural bolus dose of Dexmedetomidine and may be considered as an alternative to achieve active sedation with reduced respiratory depression which may arise on using large dose of intravenous sedatives.

In a randomized controlled study of 60 patients undergoing lower limb surgeries done by Jain D et al assessing the effects of epidural Dexmedetomidine in patients receiving intrathecal Bupivacaine, it was noted that Dexmedetomidine significantly increased the duration to 424 minutes in contrast to 140 minutes in the placebo group. Both groups received 2.5ml of 0.25% Bupivacaine intrathecally and the control group received 10ml of saline in the epidural while the Dexmedetomidine group received 2mcg/kg Dexmedetomidine made to a volume of10ml. In the Dexmedetomidine group, they observed significantly ($p=0.000$) decreased requirement of rescue analgesia and better sedation within 10 minutes of the injection and which lasted for 45-50 minutes. They observed a fall in mean arterial pressure and heart rate 5 minutes following the injection which lasted till the end of

surgery. Hence they concluded that addition of Dexmedetomidine epidurally not only prolongs the duration of analgesia and provide adequate sedation but also decreases the requirement of rescue analgesics with associated hypotension and bradycardia.

Bajwa et al[11] compared Dexmedetomidine and Clonidine as adjuvants to Ropivacaine in epidural anesthesia in patients undergoing vaginal hysterectomy. One group received 17ml of Ropivacaine 0.75% with dexmeditomidine 1.5mcg/kg and the other 17ml of Ropivacaine 0.75% with 2mcg/kg Clonidine and the block characteristics were observed. There was an early onset of sensory block in the patients receiving Dexmedetomidine as compared to Clonidine which was not statistically significant. The sedation was significantly better ($p<0.05$) in the Dexmedetomidine group when compared to Clonidine group. The mean time for two sensory dermatome regression and motor regression was prolonged in the Dexmedetomidine group. The time for first rescue analgesia was also significantly prolonged in the Dexmedetomidine group. The side effect between two groups was similar with an increased incidence of nausea and dry mouth. When compared to Clonidine, Dexmedetomidine was a better adjuvant to Ropivacaine.

A similar study was conducted by Swami et al[12] in patients undergoing upper limb surgeries, comparing 1mcg/kg Dexmedetomidine and Clonidine as adjuvants in supraclavicular brachial plexus block. Both groups were found to be comparable in terms of demographic profile, type and

duration of surgery. There was a significantly longer duration of motor and sensory blockade in the group of patients receiving Dexmedetomidine as compared to the group receiving Clonidine. It was also found that, there was a significant increase in the duration of analgesia in the Dexmedetomidine group in comparison to the Clonidine group. The quality and intensity of block was higher in Dexmedetomidine group than in the Clonidine group. Hence they concluded that Dexmedetomidine increased both the quality and the duration of brachial plexus block in comparison with Clonidine when used as an adjuvant to Ropivacine.

A comparative study of caudal Dexmedetomidine at 1mcg/kg and Clonidine at 1mcg/kg as adjuvant to 0.25%Bupivacaine in children undergoing below umbilicus surgeries done by Raval et al showed significantly better block characteristics in children receiving Dexmedetomidine Children were administered caudal anaesthesia with 1ml/kg of 0.25% Bupivacaine with 1mcg/kg of the study drug (Clonidine or Dexmedetomidine) was given. An increase in pulse rate and blood pressure of more than 20% to surgical incision was considered failure of caudal blockade. Post operatively patients were monitored for changes in heart rate, blood pressure and saturation and analgesia was assessed using the CRIES scale. The duration of analgesia in children receiving Dexmeditomidine was 14±1.6 hours in comparision to Clonidine which was 11±2.4 hours. There was however, no significant difference in the hemodynamic changes between the 2 groups.

El-Hennawy[28] et al compared the effects of Clonidine and Dexmedetomidine as adjuvants to Bupivacaine in caudal anaesthesia. Caudal anaesthesia was induced with 0.25%Bupivacaine at 1ml/kg with 2mcg/kg of either Dexmedetomidine or Clonidine. They found no significant difference between the two groups in terms of duration of analgesia hemodynamic profile and side effects (p=0.796).They observed that there was no significant difference between Dexmedetomidine and Clonidine as adjuvants to local anaesthesia.

In a recent meta analysis, Abdulla & Brull[(29)], who reviewed nine randomized control studies to determine if, Dexmedetomidine when used as an adjuvant to local anesthesia alone, causes prolongation of analgesia. They inferred that unlike Clonidine, which increases the duration of only short acting local anaesthetics, Dexmedetomidine clearly prolonged the duration of block of long acting local anaesthetics. They also suggested that Dexmedetomidine may not produce preferential sensory block like Clonidine, which may be a disadvantage as it can delay rehabilitation. There was no obvious association between Dexmedetomidine and the incidence of hypotension or respiratory depression, however felt that most studies are were not aimed at determining the safety of demedetomidine and long terms studies required to efficiently assess the safety of Dexmedetomidine as no study was able to justify the compatibility or safety of the combination of local anaesthetics with Dexmedetomidine. Hence they concluded that there is

currently insufficient data in the clinical setting to support the advantage and safety of perineural and neuraxial Dexmedetomidine with local anaesthetics.

Ropivacaine is a long-acting local anaesthetic, with a low lipid solubility and a high pKa which blocks nerve fibres involved in pain transmission (A delta and C fibres) to a greater degree than those controlling motor function (beta fibres). The drug was less cardiotoxic than equal concentrations of racemic Bupivacaine but more so than Lidocaine (Lignocaine) and its threshold for CNS toxicity is significantly higher than racemic Bupivacaine in healthy volunteers (mean maximum tolerated unbound arterial plasma concentrations). Extensive clinical data have shown that epidural Ropivacaine 0.2% is effective for the initiation and maintenance of labour analgesia, and provides pain relief after abdominal or orthopaedic surgery especially when given in conjunction with opioids (coadministration with opioids may also allow for lower concentrations of Ropivacaine to be used). The drug had efficacy generally similar to that of the same dose of Bupivacaine with regard to pain relief but caused less motor blockade at low concentrations. Lumbar epidural administration of 20 to 30ml Ropivacaine 0.5% provided anaesthesia of a similar quality to that achieved with Bupivacaine 0.5% in women undergoing caesarean section, but the duration of motor blockade was shorter with Ropivacaine. For lumbar epidural anaesthesia for lower limb or genitourinary surgery, comparative data suggest that higher concentrations of Ropivacaine (0.75 or 1.0%) may be needed to

provide the same sensory and motor blockade as Bupivacaine 0.5 and 0.75%. In patients about to undergo upper limb surgery, 30 to 40ml Ropivacaine 0.5% produced brachial plexus anaesthesia broadly similar to that achieved with equivalent volumes of Bupivacaine 0.5%, although the time to onset of sensory block tended to be faster and the duration of motor block shorter with Ropivacaine. Ropivacaine had an adverse event profile similar to that of Bupivacaine in clinical trials. Several cases of CNS toxicity have been reported after inadvertent intravascular administration of Ropivacaine, but only 1 case of cardiovascular toxicity has been reported to date. The outcome of these inadvertent intravascular administrations was favourable. Ropivacaine is a well tolerated regional anaesthetic with an efficacy broadly similar to that of Bupivacaine. However, it may be a preferred option because of its reduced CNS and cardiotoxic potential and its lower propensity for motor block.[38]

Ropivacaine is a new amide local anaesthetic, which is the first commercially available in its category as a pure S-(-) enantiomer. In most recent studies, Ropivacaine exhibited a very close pharmacodynamic profile to equipotent doses of Bupivacaine. Concentrations of 0.5%, 0.75% and 1% (5, 7.5 and 10 mg/mL, respectively) Ropivacaine are used for intraoperative anaesthesia, while the concentration of 0.2% is preferred for postoperative analgesia, either alone or in combination with opioids and/or Clonidine. Ropivacaine is responsible for excellent postoperative analgesia following

epidural and peripheral perineural injections, using single-shot injections and continuous infusions. Differential sensory/motor block is only apparent at low concentrations (0.2% and less). A significant amount of recent literature focuses on its use for peripheral blocks of the lower limbs, i.e, sciatic and femoral nerve blocks. The primary benefit of Ropivacaine is its lower toxicity, mainly lower cardiotoxicity, following accidental intravascular injection. This higher therapeutic index leads to an improved safety profile as compared with potent local anaesthetics such as racemic Bupivacaine. For that reason, Ropivacaine is a good choice for both intraoperative and postoperative regional anaesthesia and analgesia.[39]

Caudal ropivacine has been shown to cause less motor blockade and longer duration of analgesia in the postoperative period than Bupivacaine in children. This study was undertaken to compare the total venous plasma concentrations of similar doses of Ropivacaine and Bupivacaine following caudal administration.

The plasma concentrations of Bupivacaine were significantly lower than for Ropivacaine at 60, 90 and 120 min after the block Absorption and tissue distribution of Ropivacaine is slower than for Bupivacaine following caudal administration in children.[40]

The study was designed to evaluate the clinical efficacy and motor blockade properties of the drug when used in lower volumes and higher concentrations of plain substances. In a randomised, double-blind study plain

Ropivacaine (ro) 1% (150 mg) and Bupivacaine (bu) 0.75% were compared in 44 patients. In the lateral position, epidural anaesthesia was performed at L2/3 or L3/4 using the loss-of-resistance technique. A test dose of 3 ml was given followed by 12 ml (total volume 15 ml). Sensory blockade was registered by the pin-prick method after 2 min at 5 min intervals up to maximal levels and after the operation at 30-min intervals. Simultaneously, the motor block was determined by means of the Bromage scale. Results are given as median values. The onset of analgesia was 6.0 min for both substances (L2), the time to level L5 16.0 and 17.0 min respectively. The median maximum upper level of sensory analgesia was achieved after 24.5 min with ro (Th 5) and after 21.0 min (Th 7) with bu. The maximum durations (regression to L2) were 321.5 (ro) and 266.0 min (bu) ($P < 0.05$). Times for 2-segment regression were comparable at 177.5 and 176.0 min, respectively, and for 4-segment regression at 201.3 and 222.0 min. Twenty-one of the 22 patients developed a first-degree motor block; 16 patients in the (ro) group developed a second-degree block, as did 14 in the (bu) group. Third-degree motor block was recorded in 3 patients. The duration of first-degree motor block was 233 min and 207 min, of second-degree block 150 and 155 min, and third-degree block 135 min in both groups. The mean arterial pressures and heart rates did not differ. The diastolic pressures were lower after (bu) than after (ro) at 30 min. No major side effects were observed. Theodrenaline and/or dihydroergotamine (1:10 diluted) was administered to 38.6% of the patients; 34.1% received

atropine for the treatment of bradycardias and hypotension of more than 20%. No significant differences were found in frequency of analgesia (pin-prick) between both groups. One of 22 patients in the ro group and 6 of 22 in the bu group required additional analgesics or general anaesthesia. With 2 patients after ro and 4 patients after bu the relaxation was insufficient for good operating conditions. Ropivacaine 1% produced a longer duration of analgesia and better clinical efficacy than Bupivacaine 0.75%. The clinical difference in motor blockade was not statistically significant. The Bromage scale is not representative for a substance with good analgesic effects and moderate motor blocking properties as has been shown in sophisticated studies on Ropivacaine motor blockade.[41]

Bupivacaine and Ropivacaine both have been shown to be effective equally in providing sensory block for lower extremity surgery through epidural route, but they both have never been compared for the ability to produce abdominal wall relaxation. A randomized study done on 18-70 years old undergoing elective gynecologic surgery, in an institutionally approved protocol. Some received a single injection of 20 ml 0.75% of Bupivacaine at the interspace (L2-L3-L4) and some received 20 ml 0.75% of Ropivacaine in a similar manner. Sensory block was tested using pinprick; motor block was tested with a modified Bromage scale, and rectus abdominis muscle (RAM) test and also surgeon's satisfaction. Time to achieve peak sensory block and peak sensory level were similar in both the groups. However, the time to

complete sensory regression was longer with Bupivacaine than with Ropivacaine. Bupivacaine's motor block onset in the lower extremity was significantly faster than Ropivacaine. Time to peak lower extremity motor block was shorter with Bupivacaine than with Ropivacaine. Duration of lower extremity motor blockade was longer with Bupivacaine than Ropivacaine. There were no significant difference between the two groups of drug for changes in RAM scores. Peak motor block scores using the modified Bromage score and surgeon's satisfaction with the operating conditions also did not have a significant difference between the two groups.[42] Both (0.75% Ropivacaine and 0.75% Bupivacaine) provide adequate surgical anaesthesia for lower abdominal surgery when administered via epidural route. However, lower extremity motor blockade with Ropivacaine is significantly shorter with slower onset and sensory blockade shorter at these concentrations than Bupivacaine.[43]

Kampe et al., (1999) assessed the analgesic efficacy of Ropivacaine 0.1% with or without Sufentanyl 1µg/ml in a prospective randomized double blind study involving 30 ASA I-III patients undergoing elective hip replacement surgery with epidural infusion at 5-9 ml/hour. They found that motor blockade was negligible in both groups and addition of Sufentanyl 1microgrm/ml to Ropivacaine 0.1% decreased the opioid requirement by six folds.[18]

Berti et al., (2000) in a Prospective, randomized, double-blind study involving 32 patients evaluated the effects of addition of low dose Fentanyl (2 microgram/ml) to either 0.2% Ropivacaine or 0.125% Bupivacaine on

postoperative analgesia through PCA pumps after major abdominal surgery. They used a basal epidural infusion of 4ml/hour with incremental dose of 1.5ml and 20 minutes lockout interval. They found no differences in pain relief, motor block, degree of sedation and recovery of gastrointestinal motility between the two groups. However they reported the request for incremental doses and more analgesic solution consumption in patients receiving Ropivacaine alone than patients receiving the Ropivacaine/ Fentanyl mixture and also a significant decrease in peripheral SpO2, lasting up to 48 hours after surgery in the latter group. They concluded that 0.2% Ropivacaine with or without Fentanyl provided adequate pain relief in most patients with a very low degree of motor blockade and adding 2 microgram/ml Fentanyl to 0.2% Ropivacaine reduced total consumption of local anesthetic and also need for incremental doses. But there was no 10 clinically relevant advantages in quality of pain relief and incidence of motor block with addition of Fentanyl.[17]

Pouzeratte et al (2001) compared analgesic efficacy, adverse effects of Ropivacaine with Bupivacaine, both combined with Sufentanyl and also the efficacy of Ropivacaine 0.2% alone in 60 patients who underwent abdominal surgery. It was a prospective, randomized, double-blinded study. The patients were randomly allocated into three groups to receive 0.25% Bupivacaine with 1mcg/ml Sufentanyl 0.25%

Ropivacaine with 1mcg/ml Sufentanyl and 0.75% Ropivacaine alone intraoperatively. This was followed by 0.125% Bupivacaine with 0.5mcg/ml

Sufentanyl, 0.125%Ropivacaine 0.5mcg/ml Sufentanyl and 0.2% Ropivacaine alone for postoperative analgesia. They found that the local anaesthetic consumption was less among Bupivacaine with Sufentanyl group when compared with that of Ropivacaine with Sufentanyl and Ropivacaine alone (P = 0.0003 and P =0.0003, respectively). Addition of Sufentanyl to Ropivacaine optimized its analgesic efficacy as denoted by decreased consumption of local anaesthetics in Ropivacaine with Sufentanyl group. They concluded that addition of 0.5 mcg/ml Sufentanyl to 0.125% Ropivacaine provided more effective postoperative epidural analgesia than 0.2% Ropivacaine alone. In combination with Sufentanyl, Ropivacaine was less potent than Bupivacaine by a factor of 0.75% in reliving the pain[(21)]

Kida K, et al in 2008 conducted a study to determine whether intraoperative systemic Dexmedetomidine improves postoperative pain and interacts with epidural Neostigmine to produce analgesic effects. They concluded that the intraoperative systemic infusion of Dexmedetomidine alone at doses causing sedation does not result in postoperative analgesic effects. However, the co-administration of systemic Dexmedetomidine and epidural Neostigmine at higher doses may be a useful method to improve postoperative pain management.

In 2010, Tealab, et al. studied potentiation of epidural labour analgesia using concomitant Ropivacaine and fentanyl by two doses Neostigmine. They divided 60 parturients into 3 groups and administered 0.1% Ropivacaine with

100mcg fentanyl and 0.1% Ropivacaine with 100mcg fentayl with either 500mcg or 750mcg. They noted long lasting and effective analgesia. They concluded that 500mcg Neostigmine is as effective epidurally as 750mcg.

Taspiner V, Pala Y, Diker S et al in 2012 studied pre emptive analgesia and hemodynamic efficacy of epidural Neostigmine. They concluded that pre emptive 8mcg/kg epidural Neostigmine reduced analgesic consumption with low frequency of adverse effects.

ANATOMICAL ASPECTS OF VERTEBRAL COLUMN

Anatomy holds a central position in regional anesthesia because of obvious necessity of correctly delivering the therapeutic solutions to the target neural structures.

Vertebral Bones

The vertebral column is a flexible and flexuous column, formed by series of bones called vertebrae.

The spine consists of 33 vertebrae.

- 7 cervical (C1-7)
- 12 thoracic (T1-12)
- 5 lumbar (L1-5)
- 5 sacral (S1-5 fused into one)
- 4 coccygeal (often fused into one)

The upper 3 regions remain distinct throughout life, and are known as true or movable vertebrae; those of the sacral and coccygeal are termed fixed or false vertebrae. Although the vertebrae differ in design at different levels of vertebral column, common elements can be defined.

The cervical, thoracic and lumbar vertebrae have certain differentiating features. Cervical vertebrae differ from the thoracic and lumbar vertebrae in having foramina in their transverse process. The thoracic vertebra differs from the lumbar and cervical vertebrae in that they have articular facets for ribs on their bodies.

Atypical lumbar vertebra is made up of the following parts:

1. The body
2. Vertebral arch
3. Transverse processes
4. Spinous process
5. Superior and inferior articular processes.

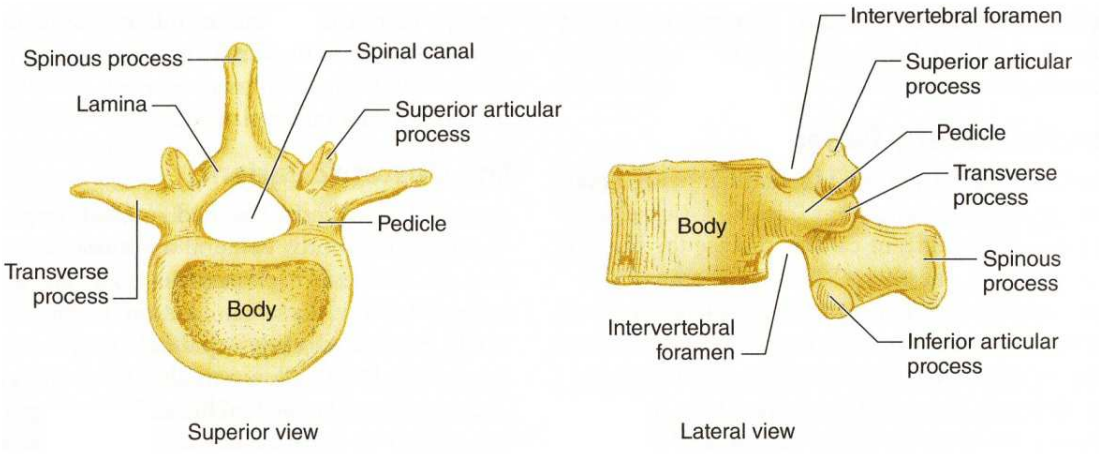


Fig 1. Parts of Vertebral Bone

Body:

It is kidney shaped. They are weight bearing. The flat articular surfaces are covered with hyaline cartilage, which is firmly united to the fibrocartilagenous intervertebral discs (annulus fibrosus and nucleus pulposus). The anterior and posterior longitudinal ligaments reinforce the union the between the bodies. The broad anterior longitudinal ligaments is firmly attached to the intervertebral discs and loosely attached to bodies. The posterior longitudinal ligament is narrower and is similarly attached.

Vertebral arch:

It is composed of pedicles and laminae, that surround the spinal cord and its coverings and protect it. Each half of the vertebral arch is divided into two parts by the root of the transverse process. Anteriorly, the arch is formed by the powerful rounded pedicle whose function is to transmit stress. Posteriorly, it is completed by the lamina, which is flat and is mainly protective in function. From the vertebral arches 4 articular processes project, 2 upward and 2 downward to articulate with similar processes of the adjacent vertebrae.

Transverse processes:

They are two in number. They are thin and long. They act as levers for muscles and ligaments particularly concerned in rotation and lateral flexion.

Spinous process:

It is almost horizontal, quadrangular and thickened along its posterior and inferior borders. They act as levers for muscles which control posture and active movements of the vertebral column.

Spinous processes of the cevical, the first two thoracic, and the last four lumbar vertebrae are all particularly horizontal and are therefore opposite the bodies of their respective vertebrae. The other spinous processes are inclined in the downward direction, with their tips opposite the bodies of the vertebrae below. Exception is the tip of the first lumbar spinous process, which is opposite the intervertebral disc.

Superior and inferior articular processes:

The superior articular processes spring from the junctions of pedicles and laminae. They project upwards behind the pedicles and come to lie just above the level of transverse processes and the articular facets on their posterior surfaces face backwards and medially. The inferior articular processes extend downwards from the infero lateral aspects of the laminae. They lie below the level of the transverse process and the articulate with the facets on the superior articular processes of the vertebra below.

Intervertebral Foramina:

The lateral aspect of the vertebral column presents a series of intervertebral foramina through which the spinal nerves and accompanying vessels passes. It provides passage between the paravertebral space and the vertebral canal.

The areolar tissue around these foramina is soft and loose in the young individual and the anesthetic solution and catheter may also pass through one of these foramina. For this reason lesser amount of local anesthetic solution is required to produce an epidural block in the elderly as compared to young individuals.

The sacral and coccygeal vertebrae fuse at puberty. Marellously exact system of ligaments, interposed cartilages and muscles at with synergestic and antagonistic precision to hold these vertebrae together and to keep the vertebra column from collapsing.

There are 4 anatomical curvatures in the vertebral column of which, the thoracic and the sacral are primary and concave anteriorly and the cervical and the lumbar are secondary and convex anteriorly. These curves have a significant influence on the spread of local anesthetic in the sub arachnoid and the epidural space.

LIGAMENTS:

The vertebral column is bounded together by several ligaments, which gives it stability and elasticity

1. The Supraspinous ligament
2. The Interspinous ligament
3. The Ligamentum flavum
4. The Anterior longitudinal ligament and
5. The Posterior longitudinal ligament

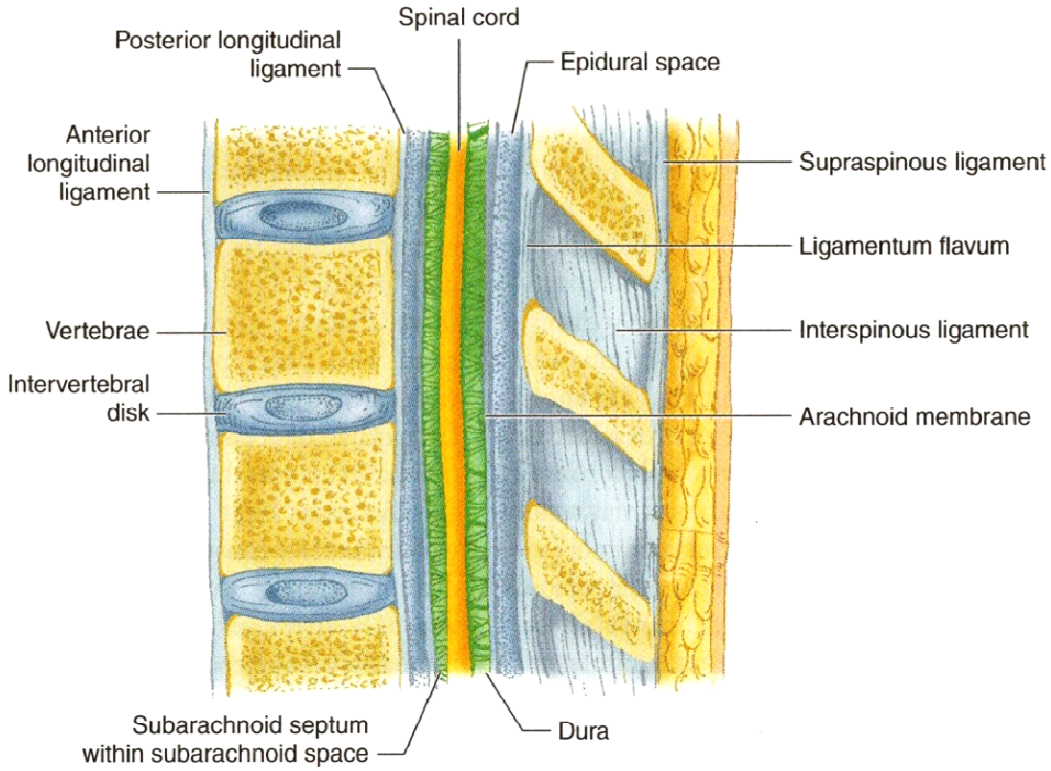


Fig 2. Boundaries of Epidural Space

Supraspinous Ligament

It is a strong thick fibrous band connecting the apices of the spines from the 7th cervical vertebra of the sacrum. At lumbar region it is thick and broad. In cervical region, it blends into the neck ligaments, where it is specialized as the ligamentum nuchae and extends from 7th cervical vertebra to occipital protuberance.

Interspinous Ligament

It is a thin fibrous structure connecting adjacent spines. The fibres are almost membraneous and extends from the apex and upper surface of the lower spine towards the root and inferior surface of the next higher vertebrae.

They meet the supraspinous ligament posteriorly and tend to blend with ligamentum flavum in front.

Ligamentum Flavum

It consists of yellow elastic tissues. The fibres are perpendicular in direction. They extend from the anterior inferior surface of upper lamina downward to the anterior superior surface of lower lamina. Ligament exsist as a right and left half. Internal surface of left and right ligamentum flavum form an acute angle with its vertex in contact with the interspinous ligament. The dorsomedian connective tissue band extends from the apex of the ligamentum flavum and the periostium through the extradural space to the spinal dura matter.

Posterior Longitudinal Ligamnent

Runs within the vertebral canal and posterior surfaces of body of vertebrae from which it is separated by the basivertebral veins.

Anterior Longitudinal Ligament

Runs along the front of vertebral bodies, it is adherent also to the intervertebral discs.

Spinal Meninges

The spinal cord is ensheathed by three membranes from without in

Dura mater: spinal dura mater; represents only the inner or meningeal layers of cerebral dura mater: the outer or endosteal layers, being represented by the

extradural space. It is connected by fibrous slips to posterior longitudinal ligament, especially near lower end of vertebral canal. A strong fibrous layer forms a tubular sheath attached above to margins of foremen of magnum and ending below at lower border of second sacral vertebra.

Arachnoid mater: this is a thin transparent sheath closely applied to the dura it surrounds the cranial and spinal nerves as far as their point of exit from the skull and vertebral canal.

Pia mater: this is separated from the arachnoid by the sub arachnoid space, filled with cerebrospinal fluid. The pia mater closely invest the cord and sends delicate septa into its substance. From each lateral surface of the piamater a fibrous band, the denticulate ligament, projects into the subarachnoid space, and is attached by a serious of pointed processes to the dura as far down as the first lumbar nerve. Pia mater ends as a prolongation, the filum terminate which pierces the distal end of the dural sac and is attached to the periostium of the coccyx.

Denticulate ligaments- the denticulate ligaments are folds of the pia mater that extend laterally along the lines of attachment of the anterior and posterior roots and fuse with the arachnoid and dura mater. Structurally, they acts as struts to hold the spinal cord suspended within the dural space. The mechanical property of these ligaments is one of elasticity and is under a stress- stress modulus 3-5 gms.

NERVE SUPPLY OF MENINGES

The posterior aspect of the dura and arachnoid contains no nerve fibres and so no pain is felt on dural puncture. The anterior aspect is supplied by spinovertebral nerves. Each of these enters the intervertebral foramen and passes up for one segment and down for 2 segments.

Spinal nerves:

These are 31 pairs in number and are as follows:

1. 8 cervical
2. 12 thoracic
3. 5 lumbar
4. 5 sacral
5. 1 coccygeal

Anterior root: is efferent and motor. Sympathetic pre ganglionic axons arise from cells in the intermediolateral horn of the spinal cord from T1 to L2.

Posterior root: is larger than anterior. All the afferent impulses from whole body including viscera pass into the posterior roots.

Each posterior roots has a ganglion and conveys fibers of 1.pain 2.Tactile, 3.Thermal, 4.Deep or muscle sensation from bones, joints, tendons etc, 5.Afferent from the visera and 6.Vasodilator fibres.

The anterior and posterior roots each with its covering of pia, arachnoid and dura cross the extra dural space and unite in the intervertebral

foramina to form the main spinal nerve trunks, which soon divide into anterior and posterior primary divisions-mixed nerves.

EPIDURAL SPACE

Definition:

Epidural space is a potential space, ellipitical, surrounds the dural sac, that extends from the foramen magnum to the coccyx and laterally, communicates with the paravertebral space through the intervertebral foraminae.

Boundaries: the epidural space is bounded superiorly by the foremen magnum where the periosteal and spinal layer of dura fuse, inferiorly by the sacrococcygeal membrane, anteriorly by the posterior longitudinal ligament covering the posterior aspect of the vertebral bodies and the intervertebral discs, posteriorly by the ligamentum flavum and the anterior surface of the vertebral laminae, and laterally by the pedicle of the vertebrae and the intervertebral foramina.

EPIDURAL SPACE ANATOMY

This space is more extensive and distensible posteriorly, while in the anterior aspect, the dura adheres closely to the periosteum of the vertebral bodies. The epidural space communicates laterally with the paravertebral space through the intervertebral foramina. With advancing age, this communication may be blocked due to the increase in the connective tissue elements.

To reach the epidural space in the midline sagital plane, the following structures are to be penetrated :

- Skin
- Subcutaneous tissue
- Supraspinous ligament
- Interspinous ligament
- Ligamentum flavum

The ligamentum flavum is an important landmark for the technical identification of the epidural space during induction. The first three tissues offer little resistance to the advancing needle, but the resistance increases when the ligamentum flavum is reached. As the needle passes through this structure there is a sudden give way of the resistance. While performing epidural analgesia, it is important to recognize this point as little further advancement may result in subarachnoid penetration.

CONTENTS OF EPIDURAL SPACES:

Spinal nerve roots along with their dural cuffs, they transverse the epidural space on their way to their respective intervertebral foramina. In the cervical region these travel almost horizontally, but lower down they become more inclined owing to the discrepancy between the length of the spinal cord and the spinal canal, until the lower lumbar and sacral roots are almost vertical.

The roots vary greatly in size and thickness. The thoracic roots are thin, while the cervical and lumbosacral roots subserving the limbs are thick. The great difference in size and neural populations within the roots are interrelated. The very large diameter and high neural population of the dorsal and ventral roots of the first sacral segments are associated with great resistance to epidural blockade. Prolonged latency and poor analgesia of S1 segment are due to poor penetration of local anesthetic and it deserves a special mention as they have an important role in the mechanism of the action to epidural anesthesia.

The arachnoid villi and granulations invaginate the epidural veins in the region of the dural cuff and drain the CSF from the vessels, drain the CSF into the epidural fat, from where it is drained by lymphatics.

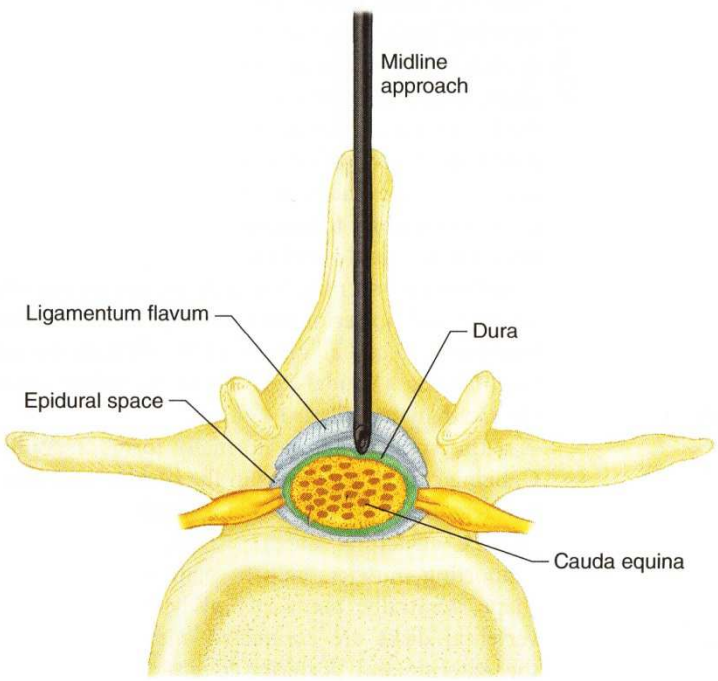


Fig 3. Midline Approach for Epidural Space

EPIDURAL VESSELS:

The branches of the subclavian, aortic and iliac arteries cross the epidural space and enter the subarachnoid space in the region of the dural cuffs. These branches provide blood supply as far as the spinal roots. Apart from the cervical region, the entire blood supply to the spinal cord passes through the epidural space.

The epidural veins are arranged in the form of longitudinal plexuses on either side of the line. They do not posses values. These veins although divided into anatomical groups, all interconnect and form a series of horizontal segmental anastomosis. They connect with intervertebral foramina and communicate with the vertebral, ascending cervical, deep cervical, intercostal, iliolumbar and lateral sacral veins. As the epidural veins have no valves they afford a connection between the pelvic veins below and the intracranial veins above.

The epidural veins become distended during coughing and straining and also when the inferior vena cava is obstructed by large abdominal tumors or in late pregnency. This distension of epidural veins diminishes the effective volume of the epidural space. Under these circumstances the requirement of the local anesthetic is markedly decreased, as a small volume of drugs tends to spread over a wide area in the epidural space.

FAT: the contents of the spinal canal lie cushioned in a packet of semifluid, lobulated fat. Solutions injected into the epidural space, track up and down

between the fatty areolar tissues. The epidural fat constitutes an important pharmacological space and depot for injected local anaesthetics and drugs and it is one of the three competitors for its share of the drug. The other two competitors being nervous tissue of spinal roots and cords and blood vessels within the spinal canal.

Drugs with high lipid solubility and lipoprotein binding charactristics will tend to enter the fat phase and remain there for a period of time, depending on their pharmacodynamics and on the briskness of the local blood flow competing for uptake. The compliance of the epidural fat varies from person to person and with age. In children and young adults it offers very little resistance.

LYMPHATICS:

Surrounding and draining the dural sac, lympatics run anteriorly from each intervertebral foramen and empty into the longitudinal channals in front of the vertebral column.

Ventrally the connective tissue is present in significant amounts, forming a strong connection between the dura mater and the anterior longitudinal ligaments in the vertebral canal. A distinct midline fold of connective tissue known as the plica mediana dorsalis of the duramater, extends in a longitudinal direction in the midline that connects the dura to the ligamentum flavum in the midline. These midline bands divide the epidural space into two sides, right and left and narrows the epidural space in the midline.

The dorsomedial connection between the dura and the ligamentum flavum can explain some of the results occurring during clinical epidural anesthesia. The epidural needle must separate the dorsomedian fold during insertion. Insertion of a catheter may result in its disposition slightly to either side of the midline. When a true dorsomedian band or membrane exists, a patchy and/or a unilateral type of block can result. The Dorsomedian connections also explain the difficulty and the effort needed to advance the epidural catheter freely into the epidural space.

SIZE OF THE EPIDURAL SPACE:

Regional epidural space width and dural thickness:

- Cervical
- Upper thoracic
- Lower thoracic
- Lumbar

IDETIFICATION OF EPIDURAL SPACE:

a) Negative pressure methods:
   - Hanging drop technique
   - Capillary tube technique
   - Manometer technique

b) Loss of resistance methods
   - Syringe technique
   - Spring loaded syringe technique

- Ballon technique
- Brooks device technique
- Vertical tube of Dawkins technique

c) Other techniques:

- Ultrasonic localization
- And the oxford- epidural space indicator.

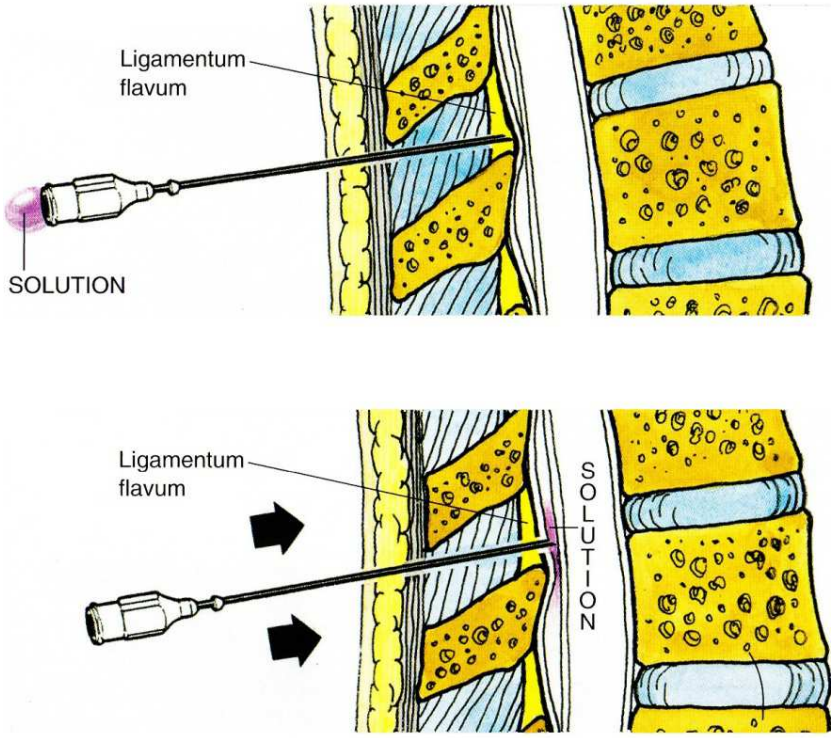


Fig. 4.Tecnicniques to find out Epidural Space

Summary of fate of injected solution in epidural space:

Local anesthetic or other agent injected into the epidural space may potentially spread as follows: superior and inferior spread is mainly in posterior portion of epidural space between dura and ligamentaum flavum.

Superiorly the spread is to magnum. There is possibility of diffusion across dura at base to cerebral CSF with possibility of blockade of cranial nerves, vasomotor and respiratory centres and other vital centres.

Inferiorly to sacral hiatus, caudal canal and through anterior sacral foramina. Laterally through intervertebral foramina to paravertebral space, to produce paravertebral neural blockade. There is rapid access to CSF at dura cuff region to produce spinal nerve root blockade and also subsequent access to spinal cord.

Anteriorly is the thin epidural space between dura and posteriorly longitudinal ligament. There is also access for injection solution to CSF by slow diffusion into the subarachnoid space. Vascular absorption by way of epidural veins may convey drug directly to brain and epidural fat also takes up the drug.

The longitudinal spread in epidural space leads to:

- Leakage by vascular absorption.
- Leakage through intervertebral foramina – paravertebral block of nerve trunks in young subjects – centripetal spread – subpial spread – spinal root and peripheral cord block.
- Diffusion through dural root sleeves – subdural spread – spinal root block.
- Diffusion through dura mater – CSF – spinal root and pheripheral cord block.

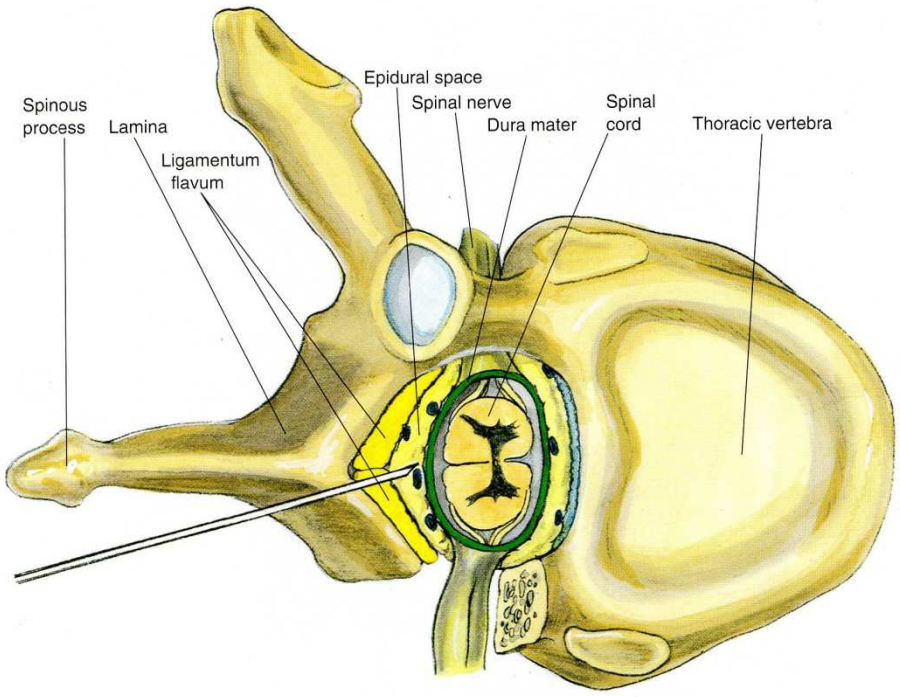


Fig 5. Paramedian Approach for Epidural Space

Factors affecting epidural spread:

- Spread increases with age: Escape from the epidural space is relatively less due to the invertebral foramina being more fixed and the epidural vessels being less penetrable.
- Spread is greater in pregnant ladies.
- In arteriosclerotic patients and patients with occlusive arterial disease the spread is greater than normal.
- Spread decreases in dehydration, shock and in cachexia.
- The extent of anesthesia is greater with concentrated solutions.
- A larger dose is required in taller individuals.

PHYSIOLOGICAL CONSIDERATIONS :

Negative pressure in the peridural space is greatest at the points of firm attachment. It is also greatest in the thoracic region, less in the lumbar region, and least or absent in the sacral area. There are two theories explaining the negative pressure are:

1. **The Cone Theory:** This theory considers that the needle introduced into peridural space depresses the dura and consequently creates a larger epidural space. It is thus considered as an artifact caused by indentation of the dura by the advancing needle.
2. **The Transmission Theory**: this theory considers that the negative pressure in the epidural space is the transmission of the intrapleural negative pressure via the intervertebral foramina to the peridural space.

EFFECTS ON ORGAN SYSTEM

Cardiovascular system :

Vasodilatation of resistance and capacitance vessals occurs, causing relative hypovolemia and tachycardia, with a resultant drop in blood pressure. This is exacerbated by blockade of the sympathetic nerve to the adrenal glands, preventing the release of catecholamines. If blockade as high as T2. Sympathetic supply to the heart(T2-T5) is also interrupted and may lead to bradycardia. The overall result may be inadequate perfusion of vital organs and measures are required to restore the blood measure and cardiac output,

such as fluid administration and the use of vasoconstrictors. Sympathetic outflow extends from T1-L2 and blockade of nerve roots below this level, as with, for example, knee surgery, is less likely to cause significant sympathetic blockade, compared with procedures requiring blockade above the umbilicus.

Respiartory system:

Usually unless blockade is high enough to affect intercostal muscle nerve supply(thoracic nerve roots) leading to reliance on diaphragmatic breathing alone. This is likely to cause distress to the patient, as they may feel unable to breath adequately.

GIT system:

Blockade of sympathetic outflow(T5-L1) to the GI tract leads to predominance of parasympathetic (vagus and sacral parasympathetic outflow) leading to active peristalsis and relax the sphincters, and a small conracted gut which enhances surgical access. Splenic enlargement 2-3 fold occurs.

Endocrine system:

Nerve supply to the adrenals is blocked leading to a reduction in the release of catecholamines.

Genitourinary tract:

Urinary retention is a common problem with epidural anaesthesia. A severe drop in blood pressure may affect glomerular filtration in the kidney if sympathetic blockade extends high enough to cause significant vasodilatation.

Materials & Methods

MATERIALS AND METHODS

This study design is comparative study.

Study setting in patients undergone lower abdominal and lower limb surgeries under epidural anaesthesia in the department of anaesthesia in Sree Mookambika Institute of Medical Sciences, Kulasekharam. The study period was 12 months.

Total sample size of 70 was selected and divided into two groups which are described below

Group I : Patients receiving 15ml of 0.75% of Ropivacaine with 1 mcg/kg of Dexmedetomidine

Group II : Patients receiving 15 ml of 0.75% of Ropivacaine with 1 mcg/kg of Clonidine

SAMPLING:

Sample size of each group: 35

Total sample size of the study: 70

Scientific basis of sample size used in the study: Formula comparative and descriptive study.

$$n = 2S^2 \frac{(Z_1 + Z_2)^2}{(M_1 - M_2)^2}$$

S_1 = Standard deviation of Dexmedetomidine = 3.96

S_2 = Standard deviation of Clonidine = 4.86

Z_1 = Z value associated with alpha = 1.64

Z_2 = Z value associated with beta = 0.84

M_1 = mean of Dexmedetomidine = 13.14

M_2 = mean of Clonidine = 15.8

Sample size = 34.34 ~ 35

sample size of Dexmedetomidine group = 35

Sample size of Clonidine = 35

Total sample size = 70

S= pooled standard deviation = 4.43

Sampling Technique: Convenient sampling.

Inclusion criteria:

- Patients giving valid consent.
- Patients under ASA (American Society of Anaesthesiology) physical status 1 and 2 (ASA 1 – normal and healthy patients, ASA 2 – patients with mild systemic disease without any functional limitation.
- Patients undergoing lower limb and lower abdominal elective surgeries under epidural anaesthesia.
- Patients aged between 18-65 years of age.

Exclusion criteria:

- Refusal by the patient.
- Patients with ASA physical status 3 or more.
- Patients posted for emergency surgeries and caesarean section.
- Patients with history of alcohol or drug abuse.
- Patients who are allergic to any of the test drugs.
- Contraindication to spinal anaesthesia.

Formulation of the drug used:

Dexmedetomidine hydrochloride as liquid for injection, (S)-4-[1-(2,3-dimethyl phenyl) ethyl]-1 H-imidazole hydrochloride. Clonidine as liquid for injection.

Dugs used : Dexmedetomidine, Dextomed, Neon laboratories. Clonidine

Dose of the drug used: 1mcg/kg Dexmedetomidine with 0.75% Ropivacaine for epidural, 150mcg Clonidine with 0.75% Ropivacaine for epidural

Frequency of the drug used: a loading dose of 1mcg/kg of Dexmedetomidine with Ropivacaine or 1mcg/kg Clonidine with Ropivacaine during intraoperative period

Route of the drug used: Epidural

Duration of the drug used: as intraoperative.

Steps taken to prevent adverse drug reaction): Stop the drug immediately.

Mode of management: Hypotension (MAP below 20% of the baseline, systolic pressure < 90mmHg) will be treated with incremental doses of Mephentermine 3mg i.v and additional RL solution as appropriate. Bradycardia (HR < 50bpm) will be treated with Atropine 0.6m.g i.v and respiratory depression (RR < 12 breaths per min) by administering supplemental oxygen – 4-6L/min.Inj. Hydrocortisone 100mg i.v stat, Inj. Pheniramine maleate 1 ampoule (45.5mg) i.m stat, Inj. Adrenaline 1:1000.

Agreement of compensation: As per the rules of this institution.

Registration with Clinical Trial Registry of India [CTRI]: Yes, registration copy attached herewith.

Clinical trial design: comparative and descriptive study.

Clinical trial done at: single site

Allocation ratio of different groups: 1:1

Randomization: Yes

Type of randomization: randomized control trial

Method used to generate random sequence numbers: randomized purposive sampling technique

Allocation concealment mechanism: not applicable

Type of blinding used: this is a comparative, descriptive study

Parameters to be studied: heart rate per min, Blood pressure in mmHg, SpO_2 in percentage.

Instruments used: Multiparameter, Schiller, made in Switzerland-India.

Procedure in brief:

After approval of the study protocol by our institutional committee, written informed consent will be taken from each patient. ASA status I and II patients of either sex, aged between 18-65 years, weighing 50-70kgs, undergoing lower limb or lower abdominal surgery under epidural anaesthesia will be enrolled in this study. All the patients will be visited on the day prior to surgery, explained in detail about the anaesthetic procedure and informed written consent will be obtained.

The patients will be kept nil orally 6hrs prior to the day of surgery. Patients with a history of alcohol or drug abuse, diabetes mellitus, cardiac cases, hypertension, COPD, psychological disease, hepatic and/or renal disease, spinal deformities or any contraindication to spinal anaesthesia (for eg: coagulation defects, infection at the puncture site, pre-existing neurological deficits in the body, etc.) and patients allergic to amide type of local anaesthetics are excluded from the study.

On arrival to the operation theatre, following insertion of an 18-G venous cannula, 500mL of Ringer Lactate was infused to the patient before epidural anaesthesia. Standard monitors like ECG, Non-invasive Blood

Pressure and SpO_2 probe was attached and baseline parameters recorded and Inj. Ranitidine 50mg i.v and Inj. Metoclopramide 10mg slow i.v half an hour before the surgery. Group I was given Dexmedetomidine 1mcg/kg with Ropivacaine epidurally, whereas Group II will be given 1mcg/kg of Clonidine with Ropivacaine epidurally. Patients will then be positioned and 15ml 0.75% Ropivacaine was administered epidurally in L3-L4 interspace through a standard midline approach using a 18-G tuohy needle and all patients will be supplemented with oxygen - 4L/min via a face mask throughout the procedure after positioning the patient. Sensory block will be assessed using sterile pin prick method in the mid-axillary line on both sides of the chest, motor block was assessed using a modified Bromage scale (grade 0 ⇾ no paralysis; grade I ⇾ unable to raise extended leg; grade 2 ⇾ unable to flex the knee, grade 3 ⇾ unable to flex the ankle)

Sensory and motor block was assessed every minute for the first 10mins and thereafter every 10mins during the surgery and every 15mins postoperatively and be recorded. The highest dermatome level of sensory blockade and motor blockade will be recorded. Recovery time for the sensory blockade is considered as two dermatome regression of anaesthesia from the maximum level; motor block duration is the time to return to grade 1on the modified Bromage scale. Postoperative pain was assessed by using the Visual Analog Scale (VAS 0 ⇾ no pain and VAS 10 ⇾ worst possible pain) at 4, 8, 12 and 24 hour. Patients with a VAS score of 3 or more was given Inj. Tramadol

50mg slow i.v. The time of patient's first request for postoperative analgesia after the surgery was recorded as duration of postoperative analgesia.

The Ramsay sedation score was used to assess sedation (1→ Anxious or agitated; 2→ co-operative and tranquil; 3→ drowsy, but responsive; 4 →asleep, but responsive to glabellar tap; 5→ asleep with a sluggish response to tactile stimulation and 6→ asleep, with no response). The score was re-evaluated every 10mins after the administration of the drug for up to 180mins and every 15mins thereafter. Score 5/6 will be considered as excessive sedation.

The vital data viz. heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SpO_2), respiratory rate (RR) was recorded immediately before and 60secs after dural puncture, every 10mins after epidural anaesthesia intraoperatively and every 15mins in the postoperative period.

STATISTICAL ANALYSIS:

1. The study parameter was entered in Microsoft excel work sheet 2013 version and data was analysed by using statistical package of social science(SPSS) trial version 20.0
2. Test of significance used – student t test
3. Level of confidence is 95%.

4.2 ASSESSMENT OF PARAMETERS

Onset of sensory analgesia was defined as time taken to achieve loss of pain sensation at T10 dermatome level from the end of injection of the study drug. This was evaluated by using pin prick along the mid axillary line at

every minute till onset of block at T10.

Duration of analgesia is defined as the time taken from the onset of sensory blockade at the T 10 level to the time of sensation of pain at the surgical site with a VAS score of >3.

Peak sensory level was defined as the highest dermatome level of sensory blockade achieved after administration of study drug.

Time to two dermatome regression was defined as the time interval from the sensory block at the highest dermatome to the regression of sensory blockade by two dermatomes. The sensory level was assessed every 15minutes after 2 hours of epidural bolus injection till 2 dermatome regression of sensory level was observed.

The time to motor blockade was defined as the time interval from the administration of epidural study drug to the achievement of grade 3 motor blockade in the lower limbs.

The degree of motor block was assessed using the modified Bromage scale.

The assessment for motor block was done every 5 minutes after administration of study drug till a block of modified Bromage grade 3 motor blockade was achieved.

The level of sedation was assessed 10minutes after grade 3 motor blockade and at the end of surgery based on the Ramsay sedation scale.

Hemodynamic parameters were monitored every 5 minutes for the first 30 minutes, every 10 minutes thereafter till the end of surgery. Patient received inj. Atropine 0.6 mg when the heart rate fell below 20%of baseline (bradycardia) and Inj. Mephentermie in titrated bolus when there was hypotension (fall below 20% of baseline). Any side effects seen after administration of study drug was noted and treated appropriately. Patient scheduled for lower abdominal and lower limb surgeries limb surgeries

Results

RESULTS

The study group consisted of 70 patients, 35 in group RC who received 15ml of 0.75% of Ropivacaine with 1mcg/kg Clonidine and 35 in group RD who received 15ml of 0.75% of Ropivacaine with 1mcg/kg Dexmedetomidine. Both groups were comparable demographically with respect to age and age distribution, height & weight characteristics. The distribution of the types of surgery and the duration of surgery was comparable between the two groups.

The onset of sensory blockade was found to be significantly shorter in the RD group along with a prolonged duration of the action ($p<0.005$). There was no significant difference found between the two groups in terms of onset of motor blockade and hemodynamic changes. Both groups had a similar incidence of hypotension and bradycardia which was not found to be significant. The side effects in both groups were minimal and comparable between the two groups.

DEMOGRAPHIC PROFILE

Table 1 Gender Distribution

Gender	Category				Total	
	Group 1		Group 2			
	N	%	N	%	N	%
Male	25	71.4	21	60.0	46	65.7
Female	10	28.6	14	40.0	24	34.3
Total	35	100.0	35	100.0	70	100.0

p=0.314

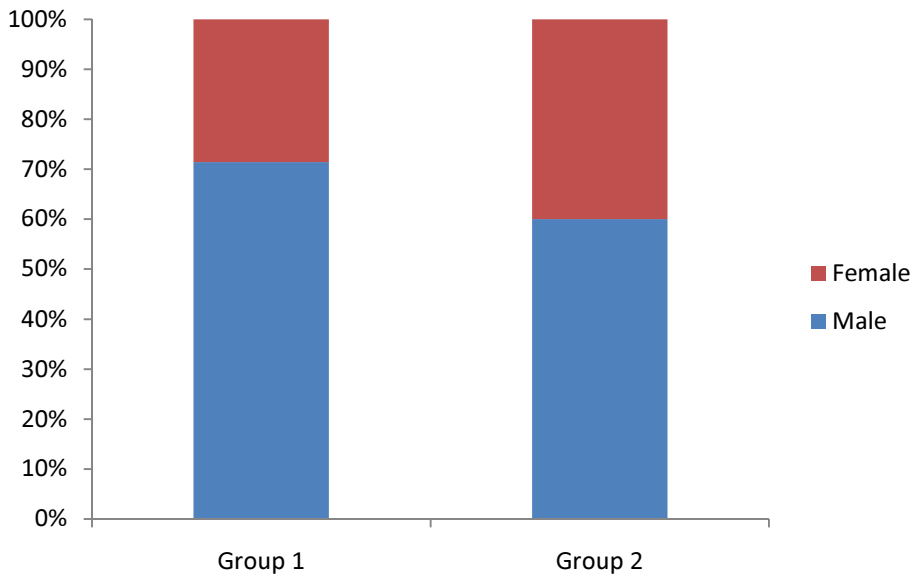


Fig 6. Gender Distribution

Gender between the 2 groups. The group RC had males of 71.4±60 and the group RD had females of 28.6±40. There was no significant difference in the gender composition between the two groups. (p=0.314)

Table 2 ASA Physical Status Distribution

ASA	Category				Total	
	Group 1		Group 2			
	N	%	N	%	N	%
Grade 1	25	71.4	27	77.1	52	74.3
Grade 2	10	28.6	8	22.9	18	25.7
Total	35	100.0	35	100.0	70	100.0

p=0.299

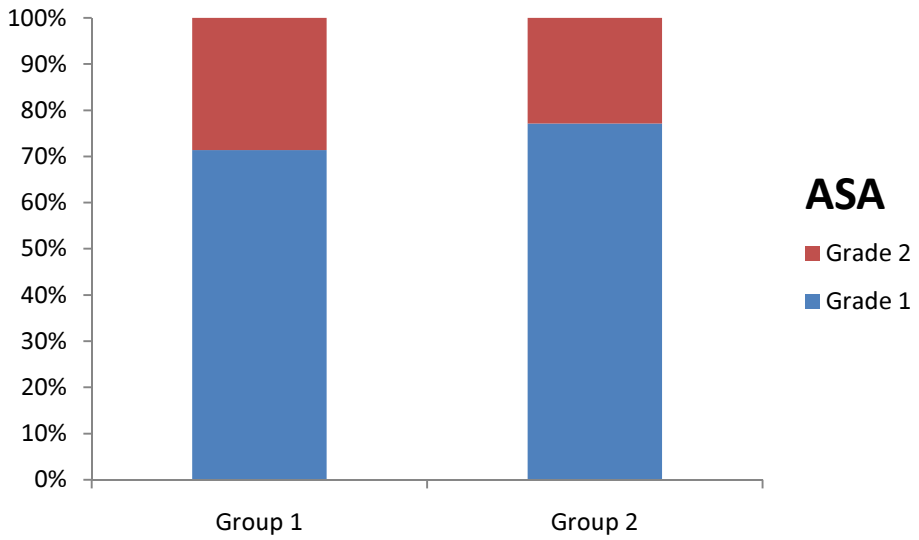


Fig 7.ASA Physical Status Distribution

ASA grading between the 2 groups. The group RC had ASA1 of 71.4±77.1 and the group RD had ASA2 of 28.6±22.9. There was no significant difference in the ASA grading between the two groups. (p=0.299)

Table 3 Weight Distribution

	N	Weight in Kg		T	P
		Mean	sd		
Group 1	35	61.14	9.239	1.199	0.235
Group 2	35	58.63	8.282		

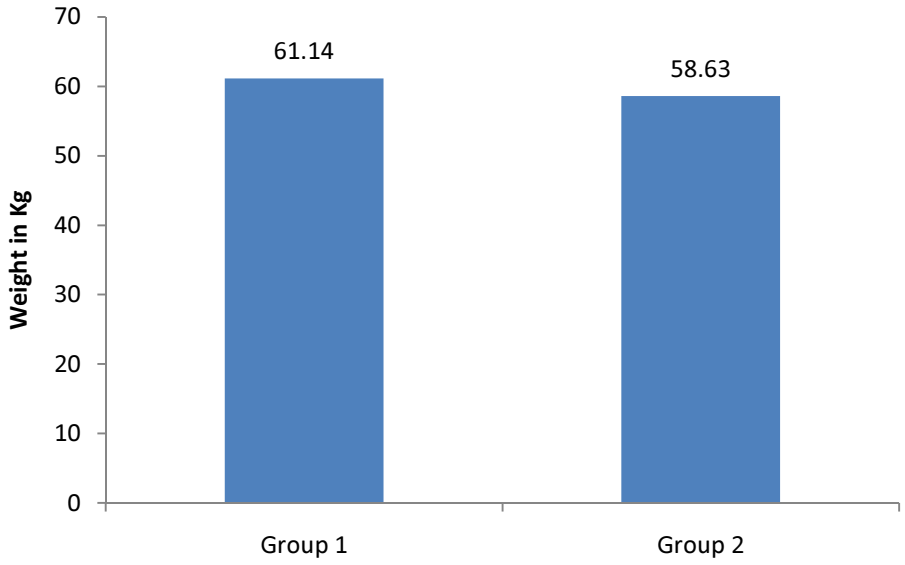


Fig 8. Weight Distribution

Weight of persons in the group RC had a mean weight is 61.14±9.239 and the group RD had a mean weight is 58.63±8.282.

Table 4 Height Distribution

	N	Height in cm		T	P
		Mean	SD		
Group 1	35	160.26	6.279	1.478	.144
Group 2	35	155.74	16.949		

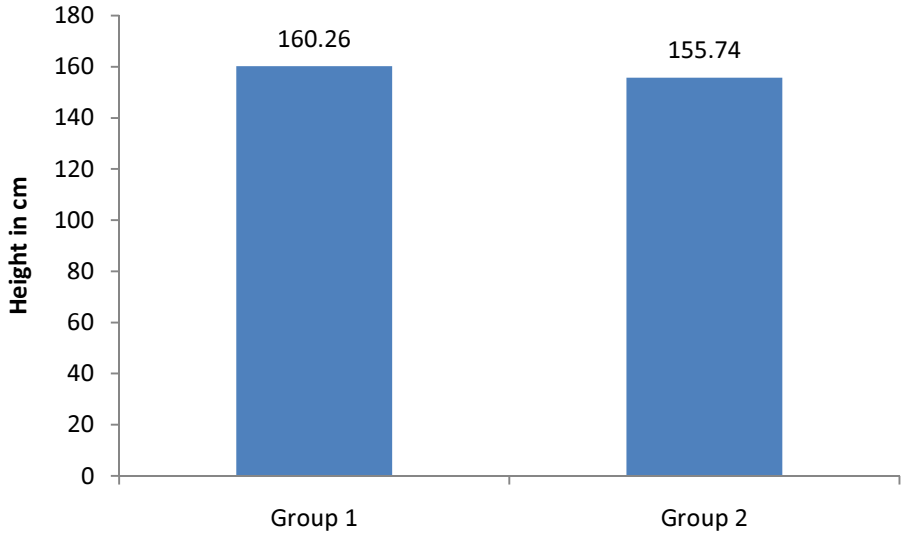


Fig 9. Height Distribution

Height of persons in the group RC had a mean height of 160.26±6.276 and the group RD had a mean height of 155.74±16.979.

Table 5 Age Distribution

	N	Age in years		t	P
		Mean	SD		
Group 1	35	41.00	9.133	-1.946	.056
Group 2	35	45.20	8.924		

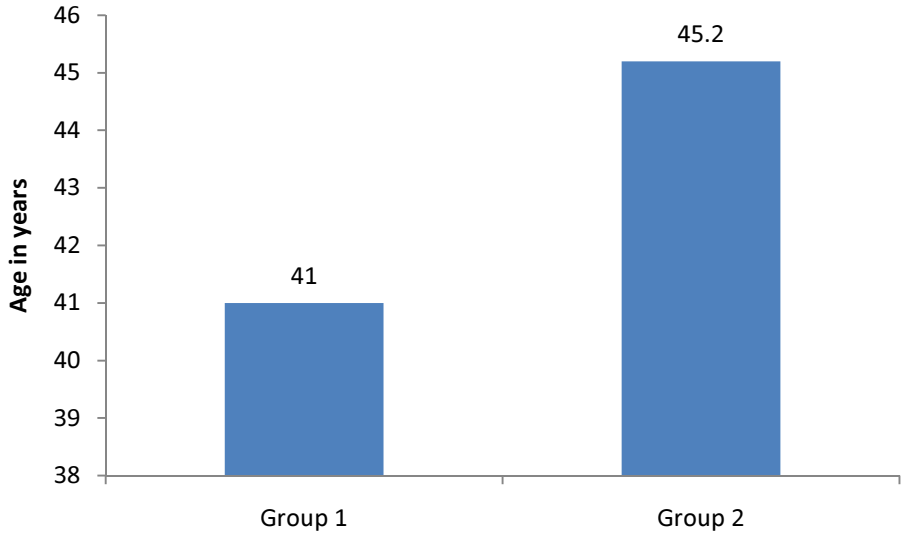


Fig 10. Age Distribution

Person between the ages 18 years to 65 years were included in this study. The group RC had a mean age of 41.00 ± 9.133 years and the group RD had a mean age of 45.20 ±8.924 years. The standard error was 1.78 in group RC and 1.65 in group RD. there was no significant difference in the age composition between the two groups. (p=0.07)

Table 6 Distribution of Surgery

Surgery	Category				Total	
	Group 1		Group 2			
	N	%	N	%	N	%
HER	20	57.1	19	54.3	39	55.7
POP	2	5.7	0	0.0	2	2.9
TIBIA	1	2.9	1	2.9	2	2.9
VH	12	34.3	15	42.9	27	38.6
Total	35	100.0	35	100.0	70	100.0

p=0.501

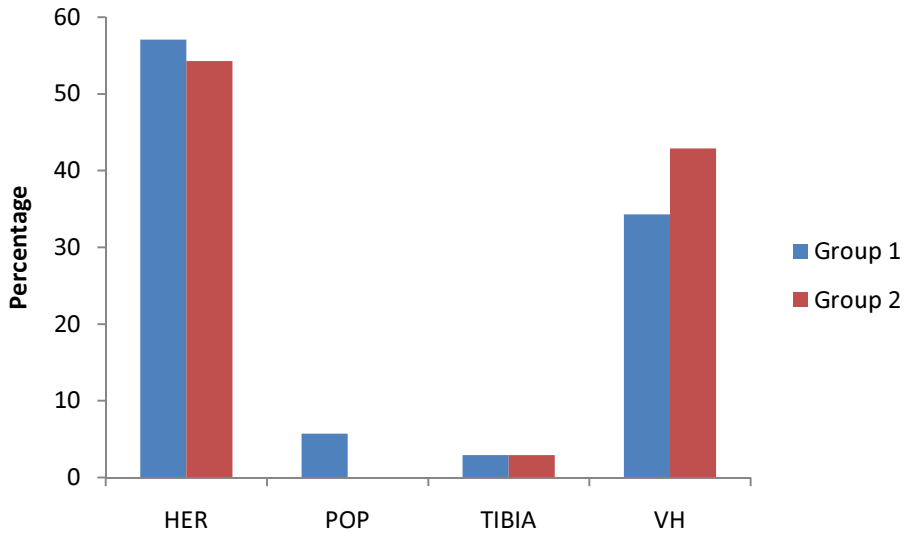


Fig 11. Distribution of Surgery

Both groups had patients undergoing hernioplasty, vaginal hysterectomies and lower limb surgeries. There was no significant difference between the two groups in terms of distribution of types of surgery, p value =0.501.

Table 7 Duration of Surgery

	N	Duration		t	P
		Mean	SD		
Group 1	35	84.00	27.675	-1.796	.077
Group 2	35	95.00	23.389		

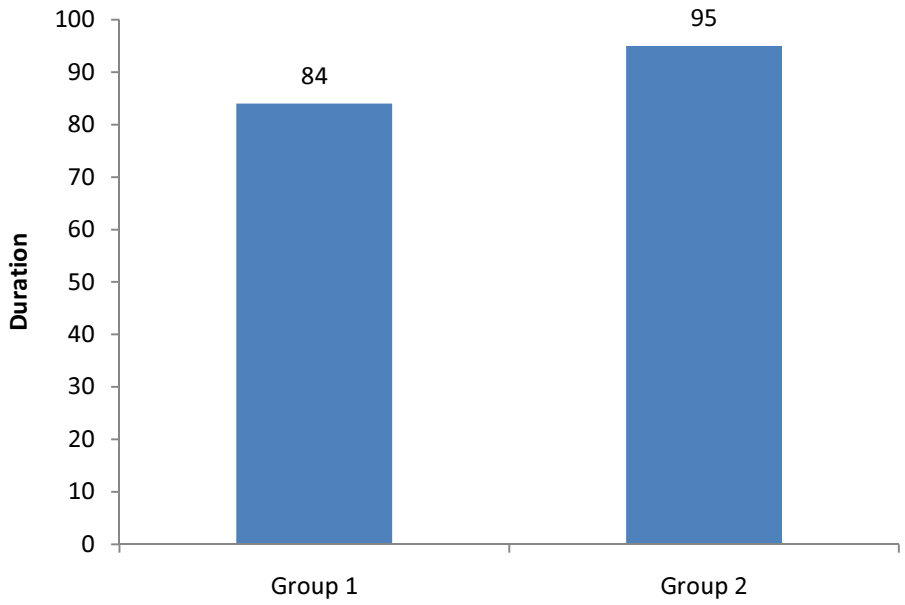


Fig 12. Duration of surgery

The mean duration of surgery in group RC is 84.00±27.675 and standard error of 4.31 and in the group RD is 95.00 ±23.389 and standard error of 4.38. The difference was statistically not significant(p=0.260)

Table 8 Efficacy of the drug

	N	T10		t	P
		Mean	SD		
Group 1	35	12.00	1.970	7.916	<0.001
Group 2	35	8.51	1.704		

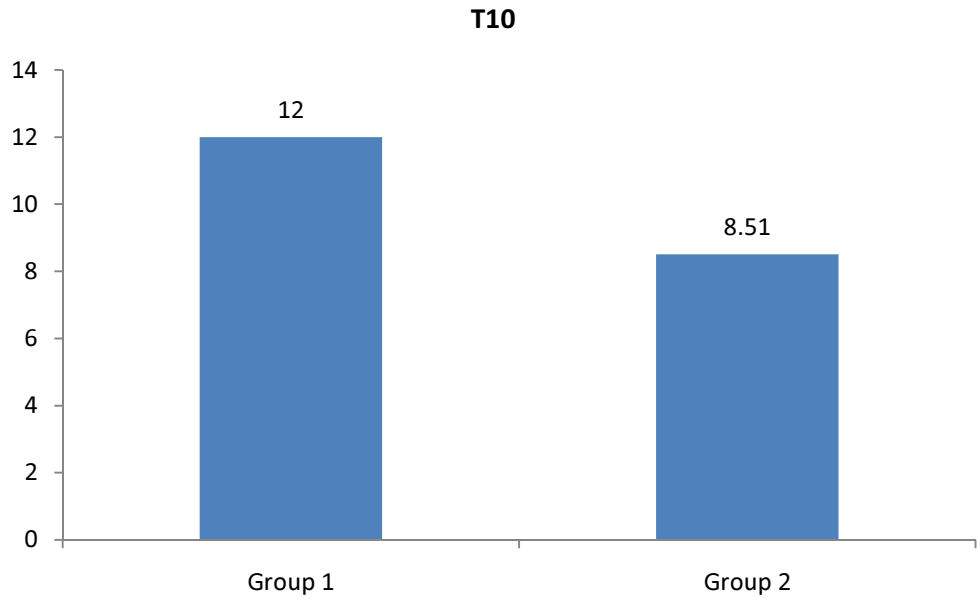


Fig 13. Efficacy of the drug

The mean time to onset on sensory blockade in group RC was 12.00 ±1.970 minutes and in group RD was 8.51 ±1.704 minutes. The difference was found to be statistically significant with a p=<0.001.

Peak level of sensory blockade

The highest level achieved in the two groups was T5, which was achieved in 5.7% of patients in the RC group and 37.1% of patients in the RD group. T6 level of sensory blockade was seen in 80.0% in the RC group and 60.0% in the RD group. The difference between the two groups is statistically significant with p=0.003

Table 9 Peak level of sensory blockade

PEAK	Category				Total	
	Group 1		Group 2			
	N	%	N	%	N	%
T5	2	5.7	13	37.1	15	21.4
T6	28	80.0	21	60.0	49	70.0
T8	5	14.3	1	2.9	6	8.6
Total	35	100.0	35	100.0	70	100.0

p=0.003

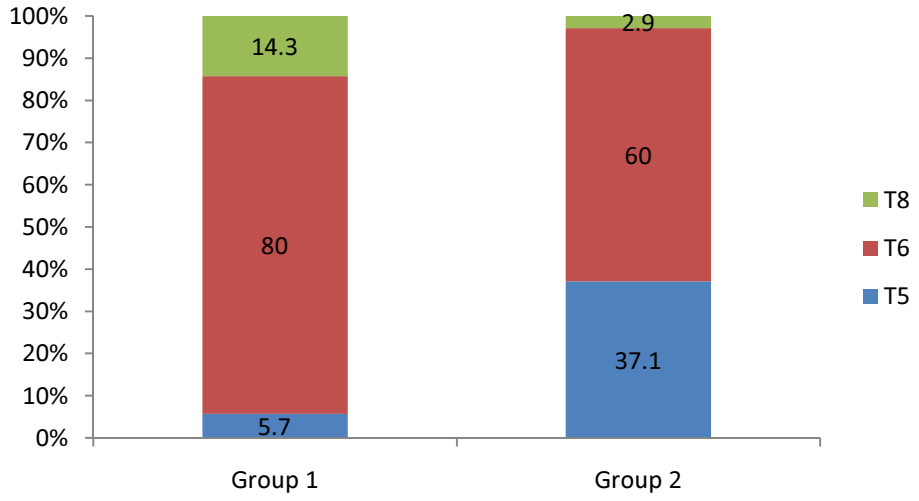


Fig 14. Peak level of sensory blockade

Table 10 Time to complete Motor Blockade (Motor Grade 3)

	N	MG_3		t	P
		Mean	SD		
Group 1	35	23.20	4.523	.195	.846
Group 2	35	23.00	4.058		

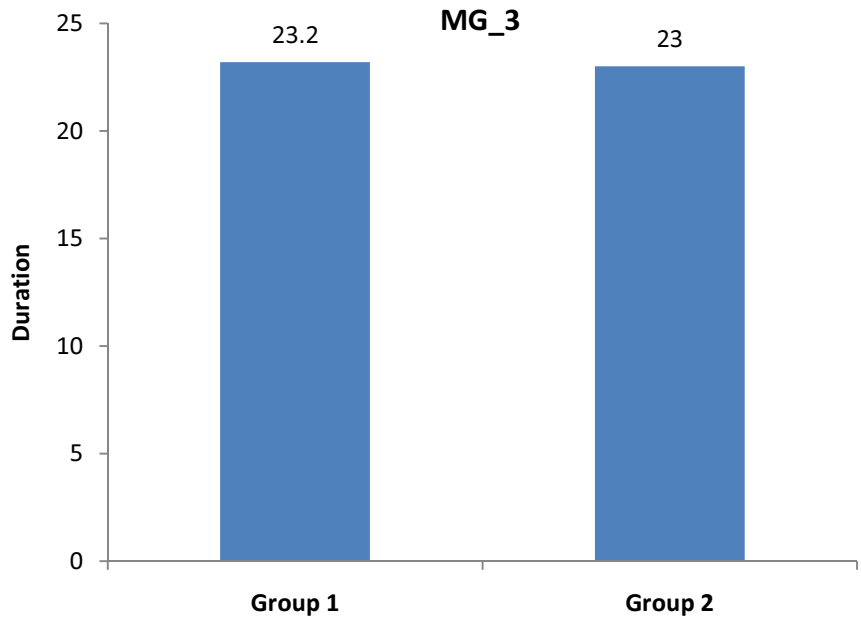


Fig 15. Time To Complete Motor Blockade

Maximum motor blockade was achieved in 23.20±4.523 minutes in group RC and 23.00± 4.058minutes in group RD. There was no statistical difference between the two groups in the onset of complete motor block with p value of 0.846.

Table 11 Duration of Blockade-Time to Rescue Analgesia

	N	Duration		T	P
		Mean	SD		
Group 1	35	275.14	40.520	-4.935	<0.001
Group 2	35	316.86	29.308		

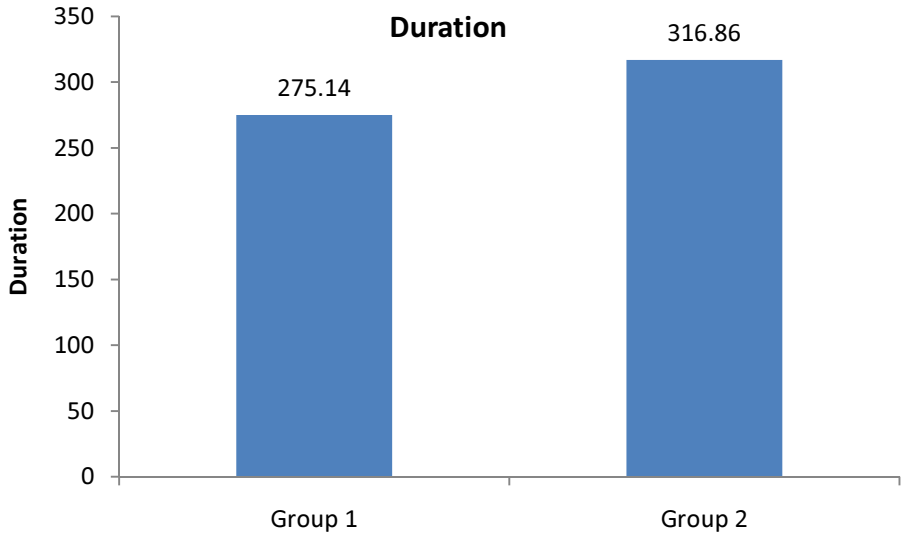


Fig 16. Duration of blockade - time to rescue analgesia

The mean duration of sensory blockade in the group RC was 275.14±40.52minutes and in group RD was 316.86±29.308minutes. There was a statistically significant difference in the duration of blockade between the two groups with a p value of <0.001.

Table 12 Time To 2 Dermatome Regression

	N	2DERM		t	P
		Mean	SD		
Group 1	35	137.00	20.227	-5.762	<0.001
Group 2	35	161.43	14.831		

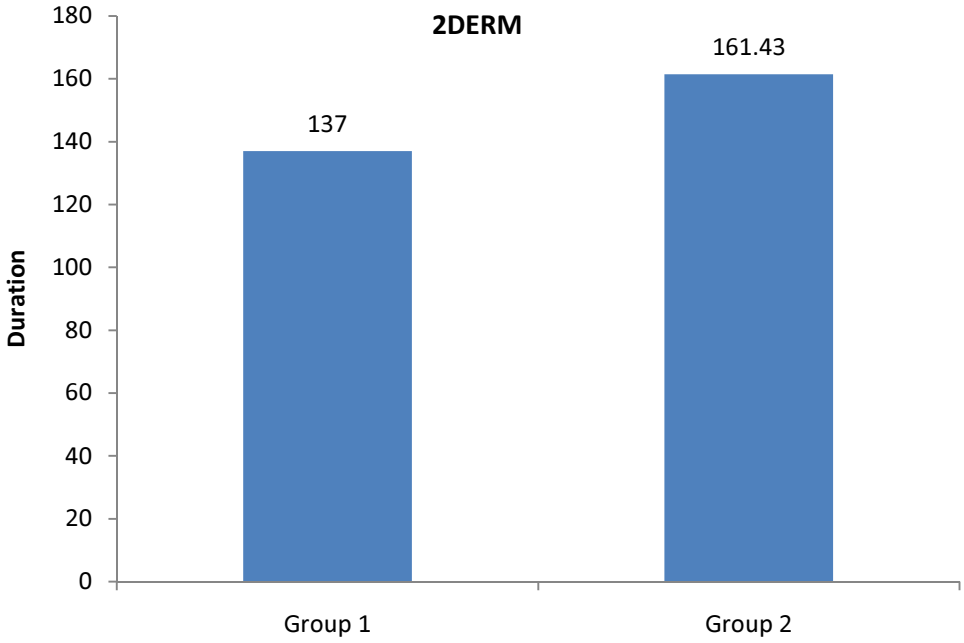


Fig 17. Time to 2 dermatome regression

The time to two dermatome regression of sensory blockade in group RC was 137 ±20.227 minutes and in group RD was 161.43 ±14.831 minutes. This difference between the two groups was found to be statistically significant. (p=<0.001).

Table 13 Sedation Score at 10 Minutes

SE_10	Category				Total	
	Group 1		Group 2			
	N	%	N	%	N	%
2	24	68.6	0	0.0	24	34.3
3	11	31.4	22	62.9	33	47.1
4	0	0.0	13	37.1	13	18.6
Total	35	100.0	35	100.0	70	100.0

p<0.001

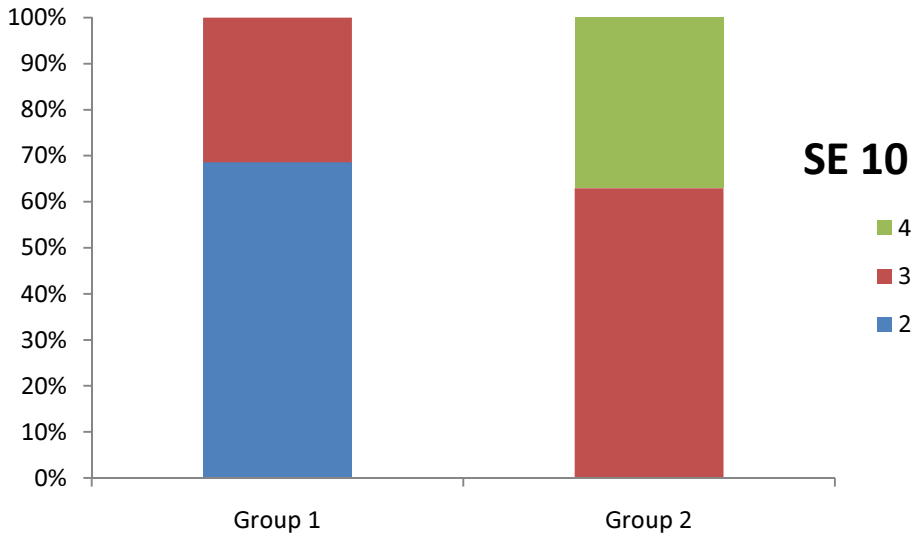


Fig 18. Sedation score at 10 minutes

Sedation was assessed 10minutes after motor grade 3 blockade using Ramsay sedation score. 24 out of the 35 cases (68.6%) in group RC had a score of 2 while 22 out of 35 cases (62.9%) in group RD had a sedation score of 3. The difference in the sedation between the two groups was found to be statistically significant. (p=<0.001).

Table 14 Sedation Score at the end of surgery

	Category				Total	
	Group 1		Group 2			
SED_END	N	%	N	%	N	%
2	25	71.4	0	0.0	25	35.7
3	10	28.6	33	94.3	43	61.4
4	0	0.0	2	5.7	2	2.9
Total	35	100.0	35	100.0	70	100.0

p<0.001

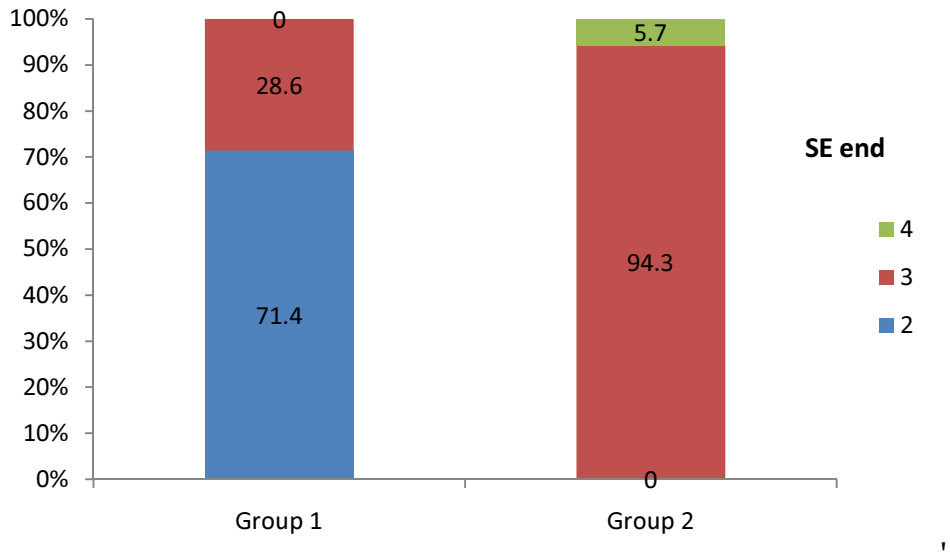


Fig 19. Sedation Score at the end of surgery

Sedation score was assessed at the end of surgery and it was found that 25 out of the 35 cases (71.4%) in group RC had a score of 2 while 33 out of 35 cases (94.3%) I a group RD had a sedation score of 3. The difference in the sedation between the two groups was found to be statistically significant. (p=<0.001)

Table 15 Changes in heart rate over time

Heart rate	Group 1 (N=35)		Group 2 (N=35)		t	P
	mean	sd	mean	sd		
0 minute	77.40	8.222	79.49	10.472	-.927	.357
5 minute	76.57	9.319	78.49	10.752	-.796	.429
10 minute	72.34	9.152	70.89	9.380	.658	.513
15 minute	66.46	13.611	67.29	8.191	-.309	.759
20 minute	64.43	6.984	62.57	7.072	1.105	.273
25 minute	61.37	7.166	60.86	6.779	.308	.759
30 minute	60.03	6.506	58.23	7.581	1.066	.290
40 minute	60.60	6.779	57.66	6.633	1.836	.071
50 minute	60.91	7.164	57.14	6.731	2.270	.026
60 minute	59.06	5.810	58.23	6.695	.553	.582
70 minute	61.31	8.025	57.43	5.468	2.367	.021
80 minute	59.17	5.591	57.57	5.164	1.244	.218
90 minute	56.20	7.136	57.60	4.894	-.957	.342
100 minute	56.94	6.145	57.54	6.075	-.411	.683
110 minute	57.03	7.115	58.09	5.564	-.692	.491
120 minute	56.03	6.066	57.80	4.378	-1.401	.166

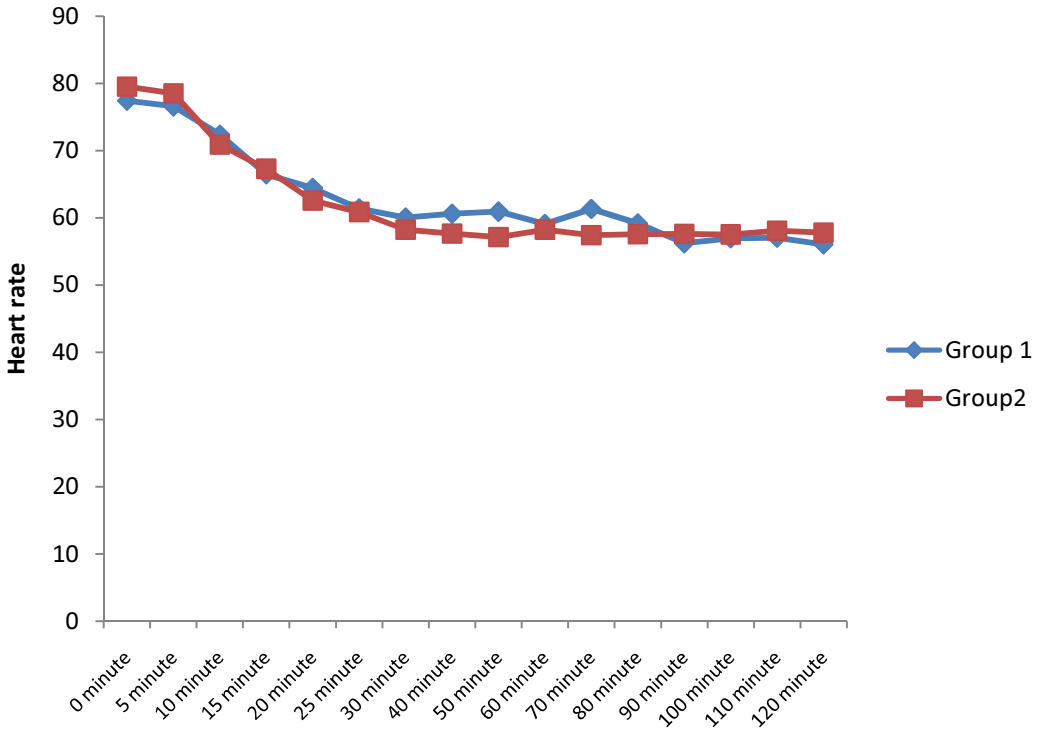


Fig 20. Changes in heart rate over time

There was a significant fall in heart rate by 20% between 30 to 50 minutes of epidural injection in both groups; however there was no significant difference in the fall of heart rate between the two groups.(p=0.592)

CHANGES IN MEAN ARTRIAL PRESSURE IN OVER TIME

There was a significant fall in the mean arterial pressure by 25% between 40 to 50 minutes in both groups, however there was no significant difference in the occurrence of hypotension between the two groups. (p=0.796).

SIDE EFFECTS

Doses of Atropine used:

The incidence of bradycardia was found to be similar in both groups and showed no statistical significance. The requirement of one dose of Atropine was 36.6% and 16.7% in group RC and RD and two doses in 3.3% and 20% I RC and RD groups respectively. There was no statistically significant difference between the two groups in term of bradycardia requiring Atropine (p=0.054).

Doses of mephentermine:

There was no significant difference in the occurrence of hypotension in both groups. The requirement of one dose of Mephentermine was 26.7% and 30% in group RC and RD groups respectively. There was no statistically significant difference between the two groups in term of hypotension requiring Mephentermine(p=0.774).

Other side effects:

There were three cases with dry mouth, two in the RC and one in the RD group no other side effects were observed during the period of our study.

Discussion

DISCUSSION

Epidural anaesthesia is considered as a gold standard technique as it provides complete, dynamic anaesthesia and post operative analgesia. The benefits include suppression of stress response by sympatholysis, stable hemodynamics with reduction in cardiac morbidity, reduction in pulmonary complications due to active physiotherapy and early mobilization, reduced blood loss and decrease in thromboembolic complications following surgery[1,2,5]

Sara et al [6] compared the characteristics of 0.75% Ropivacaine and 0.5% Bupivacaine and concluded that Ropivacaine and Bupivacaine at these doses produced equally effective anaesthesia. 0.75% Ropivacaine produce adequate intensity of motor and sensory blockade and its comparable to 0.5% Bupivacaine with reduced side effects. Hence we used 0.75% Ropivacaine to provide epidural anaesthesia.

Dexmedetomidine is known to have eight times more affinity than Clonidine for alpha adrenergic receptors, however there are no studies documenting the equivalent doses of epidural Dexmedetomidine and Clonidine[18,32,33] A number of studies have used epidural Clonidine at doses of 1-4mcg/kg ,and it has been noted that the hemodynamic side effect are dose dependent. It has been suggested that epidural Clonidine at a dose 1mcg/kg prolongs analgesia without producing unwanted side effects.

Epidural Dexmedetomidine has been studied at doses ranging from 1-2mcg/kg and it was observed that at doses less than 1mcg/kg Dexmedetomidine does not prolong the block of Ropivacaine. Hence in our study, we have used equal concentration of 1mcg/kg of Clonidine and Dexmedetomidine as an adjuvant to Ropivacaine in epidural anaesthesia.

In this study, we compared two alpha agonists Clonidine and Dexmedetomidine with 0.75% Ropivacaine in the epidural route for lower abdominal and lower limb surgeries. The study was conducted in 70 patients between the ages of 18 to 65 years who were randomly assigned into two groups. Group RD received 15ml f 0.75% Ropivacaine with 1mcg/kg of Dexmedetomidine and group RC received 15ml of 0.75% Ropivacaine with 1mcg/kg of Clonidine, both groups received a total volume of 15+ml.

The demographies of both groups were found to be comparable with respect to age, gender, height, weight & surgery duration as there was no statistically significant difference($p>0.05$)

Onset of blockade:

Our study showed significantly earlier onset of sensory blockade in the patient receiving Dexmedetomidine (8.53±1.81minutes) when compared to the patients receiving Clonidine (11.93±1.96 minutes). There was significantly higher dermatomal spread in group RD. this findings was consistent with the previous observations made by Bajwa et al[11], who found that the onset of sensory analgesia at T10 was faster in the group receiving

Dexmedetomidine (8.52±2.36min)when Compared to ten patients receiving Clonidine (9.72±3.44min) and there was also associated with a faster and higher level of sensory blockade . It has been observed that when Dexmedetomidine is administrated epidurally it reaches a maximum concentration in the CSF within 5 minutes with a distribution half life of 0.7 minutes. There is a dose dependent anti nociceptive effect of epidural Dexmedetomidine which has been associated to its affinity for the alpha 2 receptors on the spinal cord.

Dexmedetomidine also has higher lipid solubility in comparison to Clonidine. This may be the probable cause for the enhanced potency of epidural Dexdemetomidine over Clonidine.

Duration of analgesia

In this study we found that the duration on sensory analgesia was more in group RD (316±31.15minutes) than group RC (281 ± 37 minutes) which was statistically significant (p=0.000). In the study done by Sukminder Jit Singh Bajwa et al[22] , they found a significantly longer time to first rescue top up in the Dexmedetomidine group(342.88 ± 29.16minutes) than the Clonidine group (310.76± 23.76 minutes). This may be because they had also used onset of incisional pain to indicate analgesia time, however the higher doses of Dexmedetomidine (1.5mcg/kg) and Clonidine (2mcg/kg) may be considered to explain the prolonged duration in comparison to our study.

Mausumi Neogi et al studied the characteristics of Clonidine (1mcg/kg) & Dexmedetomidine (1mcg/kg) with 0.25% Ropivacaine when given caudally for post operative analgesia in children & found that the mean duration of analgesia was not significantly prolonged between the groups receiving Clonidine (13.17 ±0.68 hours) & Dexmedetomidine (13.17± 0.68hours). In their study caudal analgesia was given as an adjuvant to general anaesthesia & CRIES score of 4 above was used to denote the duration of analgesia.

Motor blockade

We found no statistically significant difference time to complete motor blockade, between the two groups, group RD in 23.00 ± 4.27 minutes & group RC in 23.07± 4.63 minutes). Bajwa et al[22] found that patients receiving Dexmedetomidne (17.24± 5.16minutes) achieved grade 3 motor blockade in less time than those receiving Clonidine (19.52 ± 4.06) as an adjuvant . This may be attributed to the larger doses of Dexmedetomidine (1.5mcg/kg) & Clonidine (2mcg/kg) used in their study.

Sedation

In this study, we found better sedation in the patients who received Dexmedetomidine that those who received Clonidine at both 10 minutes and at the end of surgery. This apparent change was also found to be statistically significant (p=0.000).

The similar study conducted by Oriol-Lopez et al,[26] assessing the anxiolytic and sedative property of epidural Dexmedetomidine in patients undergoing abdominal surgeries, Dexmedetomidine was given at a dose of 1mcg/kg. Following the injection, Ramsay sedation score was used for assessment of sedation. They found that 90% of the patients receiving Dexmedetomidine were sedated to a score of 3 to 4 for 90minutes after drug administration.

The findings of Bajwa et al[32], also showed a significantly higher level of sedation in the patients who received Dexmedetomidine in comparison to Clonidine.

These findings from the studies mentioned above concur with the findings from our study, showing that Dexmedetomidine causes significantly higher sedation that Clonidine when given epidurally.

Hemodynamic changes:

We found that heart rate significant fell in both the group by 20 in 30 to 50 minutes after the epidural injection. Blood pressure decreased by 25% in 30 to 50 minutes following epidural injection. However, this change was not statistically significant ($p>0.05$)

Similar observations were observed by Bajwa et al and Schnaider et al [34] where a 15% fall of heart rate % blood pressure from the baseline which was not statistically significant.

Side effects:

We observed similar hemodynamic changes in both the study groups. We found no significant difference in the Atropine & Mephentermine requirement as a rescue I both the groups. Findings were similar to studies done by Bajwa et al[32] & Sarita Swami et al who also found no significant difference in terms of hypotension & bradycardia between the patients receiving Dexmedetomidine or Clonidine.

Nausea, vomiting and shivering was not observed in both the groups. We had two patients in group R and one patient in group RD who had dry mouth. The study conducted by Bajwa et al showed a higher incidence of nausea, dry mouth during the postoperative period.

The limitations of our study was that as different surgeries were taken up in this study, therefore onset of pain at surgical incisional site may not give an accurate duration of analgesia. There is also need for larger studies, using different concentration of both drugs to find equivalent doses of epidural Dexmedetomidine and Clonidine. There is a further requirement to assess the long term safety and effects of epidural Dexmedetomidine as most studies only determine the short term effects.

Conclusion

CONCLUSION

We conclude that the addition of 1mcg/kg Dexmedetomidine as an adjuvant to 0.75% Ropivacaine in epidural anaesthesia causes an early onset and prolonged duration of sensory analgesia in comparison to 1mcg/kg Clonidine. Epidural dexmedetomidine cause better sedation as compared to Clonidine.

Bibliography

BIBLIOGRAPHY

1. Nimmo SM. Benefit and outcome after epidural analgesia. Contin Educ Anaesth Crit Care Pain 2004;4(2):44-7.
2. Young Park W, Thompson JS, Lee KK. Effect of Epidural Anaesthesia and Analgesia on Perioperative Outcome. Ann Surg 2001; 234(4):560-71
3. Holte K, Kehlet H. Epidural anaesthesia and analgesia- effects on surgical stress responses and implications for postoperative nutrition. Clin Nutr 2002;21(3):199-206.
4. Rigg JRA, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomized trial. Lancet 2002 Apr 13; 359(9314): 1276-82.
5. Moraca RJ, Sheldon DG Thirlby RC. The Role of Epidural Anesthesia and Analgesia in surgical Practice. Ann Surg 2003; 238(5): 663-73.
6. Chandran S, Hemalatha S, Viswanathan P. Comprison of 0.75% ropivacaine and 0.5% bupivacaine for epidural anaesthesia in lower extremity orthopaedic surgeries. Indian J Anaesth 2014;58(3):336-8.
7. Markham A, Faulds D. Ropivacaine. A review of its pharmacology and therapeutic use in regional anaesthesia. Drugs 1996; 52(3):429-49.
8. Wahedi W, Nolte H, Witte P. Ropivacaine in epidural anaesthesia. Dose-response relationship asa comparison with bupivacaine. Reg-Anaesthesia 1990; 13(3): 57-65

9. Congedo E, Sgreccia M, De Cosmo G. New drugs for epidural analgesia. Curr Drug Targets 2009; 10(8):696-706.

10. Foster JG, Rosenberg PH. Clinically useful adjuvants in regional anesthesia. Curr Opin Anaesthesiol 2003; 16(5): 477-86.

11. Bajwa SJS, Bajwa SK, Kaur J, Singh G, Arora V, Gupta S, et al. Dexmedetmidine and clonidine in epidural anaesthesia : A comparative evaluation. Indian J Anaesth 2011; 55(2):116-21.

12. Swami SS, Keniya VM, Ladi SD, Rao R. Comparison of dexmedetomidine and clonidine (α2 agonist drugs) as an adjuvant to local anaesthesia in supraclavicular brachial plexus block: A randomized double-blind prospective study, Indian J Anaesth 2012; 56(3): 243-9.

13. Eisenach J, Detweiler D, Hood d. Hemodynamic and analgesic actions of epidurally administered clonidine. Anesthesiology 1993; 7892):277-87.

14. Klimscha W, Chiari A, Krafft P, Plattner O, Taslimi R, mayer N, et al. Hemodynami and analgesic effects of clonidine added repetitively to continuous epidural and spinal blocks. Anesth Analg 1995; 80(2):322-7.

15. Castro MI, Eisenach JC. Pharmaokinetics and dynamics of intravenous, intrathecal and epidural clonidine in sheep. Anesthesiology 1980;71(3):418-5

16. Eimsenach JC De Kock M Klimscha W. alpha 2 adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). Anesthesiology 1996; 85(3); 655-74.

17. Grewal A. Dexmeditomidine: New avenues. J Anesthesiol Clin Pharmacol 2011; 27(3); 297-302.

18. Eisenach JC, Shafer SL, Bucklin BA, Jackson C, Kallio A. Pharmacokinetics and pharmacodynamics of intraspinal dexmedtomidine in sheep. Anesthesiology 1994; 80(60); 1349-59.

19. Sudheesh K, Harsoor S. Dexmedtomidine in anesthesia practice; A wonder drug? Indian J Anaesth 2011; 55(4);323-4.

20. Korula S, George GM, Ipe S, Abraham SP, Epidural anesthesia and postoperative analgesiafor bilateral inguinal mesh hernioplasty; Comparision of equipotent doses of ropivacaine and bupivacaine. Saudi J Anaesth 2011;5(3):277-81.

21. Baptista JF de A, Gomez RS, Paulo DNS, Carraretto AR, Brocco MC, Silva JJ, et al. Epidural anesthesia with ropivacaine with or without, clonidine and postoperative pain in hemorrhoidectomies. Acta Cir Bras. 2014; 29(3):201-8.

22. Bajwa SJS, Bajwa SK, Kaur J. Comparision of epidural ropivacaine and ropivacaine clonidine combination for elective cesarean sections. Saudi J Anaesth 2010; 4(2): 47-54.

23. Alves TCA, Braz JRC. Clinical evaluation of clonidine associated to ropivacaine for epidural anesthesia. Rev Bras Anestesiol 2002; 52(4); 410-9.

24. Salgado PFS, Sabbag AT, Silva PC da, Brienze SLA, Dalto HP, Modolo NSP et al. synergistic effect between dexmedetomidine and 0.75% ropivacaine in epidural anesthesia. Rev Assoc Medica Bras(1992) 2008;4(2):110-5.

25. Lin YN, Li Q, Yang RM, Mao ZX, Liu JC, Addition of dexmedetomidine to ropivacaine improves cervical plexus block. Acta Anaesthesiol Taiwan 2013; 51(2): 63-6.

26. Oriol-lopez SA, Maldonado-Sanchez KA, Hernandez-Bernal CE, Castelazo-Arredondo JA, Moctezuma RL. Epidural dexmedetomideine in regional anaethesia to reduce anxiety. Revista M exicana de Anaetesiologia 2008;31:271-77.

27. Jain D, Khan RM, Kumar D, Kumar N. Perioperative effect of epidural dex-medetomidine with intrathecal bupivacaine on haemodynamic parameters and quality of analgesia. South Afr J Anaesth Analg 2012; 8(2): 22-6.

28. El Hennawy AM, Abd Elwahab AM, Abd Elmaksoud AM, El Ozairy HS, Boulis SR. Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. Br J Anaesth 2009; 103(2):268-74.

29. Abdallah FW, Brull R. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth 2013;110(6):915-25

30. Bromage PR. Epidural Analgesia. Epidural analgesia. Saunders (W.B.) Co Ltd; 1978. p. 144.

31. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. Controlled Sedation with Alphaxalone- Alphadolone. Br Med J 1974; 2(5920); 656-9.

32. Bajwa S, Kulshrestha A. dexmedetomidine: an adjuvant making large inroads into clinical practice. Ann Med Health Sci Res 2013; 3(4):475-83.

33. Bagatini A, Gomes CR, Masella MZ, Rezer G. Dexmedetomidine: pharmacology and clinical application. Rev Bras Anestesiol 2002;52(5): 606-17

34. Schnaider TB, Vieira AM, Brandao ACA, Lobo MVT. Intraoperative analgesic effect of epidural ketamine, clonidine or dexmedetomidine for upper abdominal surgery. Rev Bras Aestesiol 2005;55(5):525-31.

35. Hoobler SW, Sagastume E. Clonidine hydrochloride in the treatment of hypertension. Am J Cardiol 1971;28(1):67-73.

36. Nik Yusoff NS, Mustapha Z, Govindasamy C, Sirajudeen KN. Effect of Clonidine (an antihypertensive drug) treatment on oxidative stress markers in the heart of spontaneously hypertensive rats. Oxidative medicine and cellular longevity 2013; 2013; 927214, ges, doi:10.1155/2013/927214

37. Faulds D. Ropivacaine: an update of its use in regional anaesthesia. Drugs 2000;60:1065-93.

38. Eledjam JJ, Ripart J, Viel E. Clinical application of ropivacaine for the lower extremity. Curr Top Med Chem 2001;1(3):227-31.

39. Ala-Kokko TI, Partanen A, Karinen J, Kiviluoma K, Alahuhta S. Pharmacokinetics of 0.2% ropivacaine and 0.2% bupivacaine following caudal blocks in children. Acta anaesthesiologica scandinavica 2000;44(9):1099-102.

40. Niesel HC, Eilingsfeld T, Hornung M, Kaiser H. Ropivacaine 1% versus bupivacaine 0.75% without a vasoconstrictor. A comparative study of epidural anesthesia in orthopedic surgery. Der Anaesthesist 1993;42(9):605-11.

41. Tuttle AA, Katz JA, Bridenbaugh PO, Quinlan R, Knarr D. A double-blind comparison of the abdominal wall relaxation produced by epidural 0.75% ropivacaine and 0.75% bupivacaine in gynecologic surgery. Regional Anesthesia and Pain Medicine 1995;20(6):515-20.

42. Berti M, Fanelli G, Casati A, et al. Patient supplemented epidural analgesia aftermajor abdominal surgery with bupivacaine/fentanyl or ropivacaine/fentanyl. CanJ Anaesth 2000; 47: 27-32.

43. Kampe S, Diefenbach C, Kanis B, Auweiler M, Kiencke P, Cranfield K. Epiduralcombination of ropivacaine with sufentanyl for postoperative analgesia after totalknee replacement: a pilot study. Eur J Anaesthesiol 2002; 19: 666.

Appendices

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES.

KULASEKHARAM

RESEARCH COMMITTEE

CERTIFICATE

This is to certify that The Research Protocol Submitted by Dr. B.M. SATHESH KUMAR

Faculty / Post Graduate from Department of ANAESTHESIOLOGY

Titled "DEXMEDETOMIDINE VS CLONIDINE as an adjuvant to 0.75% Ropivacaine for Epidural Anaesthesia in lower abdominal and lower limb surgeries in a tertiary care Centre - A Comparitive Study"

is approved by the Research Committee.

Chair Person
Prof. & H.O.D.
Dept. of Bio-Chemistry
Sree Mookambika Institute of Medical Sciences
Kulasekharam 629 161

Convenor

Prof. & H.O.D.
Dept. of Physiology
Sree Mookambika Institute of Medical Sciences
Kulasekharam 629 161

Date :

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES

(Kulasekharam (K.K District, TN)-629161, Phone No: 04651-280866, Fax No: 280740)

Institutional Human Ethics Committee (IHEC)

{CDSCO Reg No: ECR/446/Inst/TN/2013}

Ref. No: SMIMS/IHEC/2015/A/29 **Date: 17th February 2016**

CERTIFICATE

This is to certify that the Research Protocol Ref. No. **SMIMS/IHEC/2015/A/29** entitled "Dexmedetomidine vs Clonidine as an adjuvant in 0.75% Ropivacaine in Epidural Anaesthesia for Lower Abdomen and Lower Limb Surgeries in a Tertiary Care Centre- A Comparative Study" submitted by Dr. B.M. Sathesh Kumar, Postgraduate of Department of Anaesthesiology, SMIMS has been approved by the Institutional Human Ethics Committee at its meeting held on 15th December 2015.

Dr. Rema Menon. N
Member Secretary
Institutional Human Ethics Committee
Professor and HOD of Pharmacology
SMIMS, Kulasekharam (K.K District)
Tamil Nadu-629161

[This Institutional Human Ethics Committee is organized and is operating according to the requirements of ICH-GCP/GLP guidelines and requirements of the Amended Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945 of Government of India.]

CONSENT FORM

PART 1 OF 2

Dear volunteers,

We welcome you and thank you for your keen interest in participating in this research project. Before you participate in this study, it is important for you to understand why this research is being carried out. This form will provide you all the relevant details of this research. It will explain the nature, the purpose, the benefits, the risks, the discomforts,theprecautions and the information about how this project will be carried out. It is important that you can read and understand the contents of the form carefully. This form may contain certain scientific terms and hence, if you have any doubts or if you want more information, you are to ask the study personnel or the contact person mentioned below before you give your consent and also at any time during the entire course of the project.

1. **Name of the Principal Investigator**	**:**	Dr. B.M.Sathesh Kumar Postgraduate – M.D Anaesthesiology Sree Mookambika Institute of Medical Sciences, Kulasekharam
2. **Name of the Guide**	**:**	Dr. Thavamani Professor& HOD Department of Anaesthesiology Sree Mookambika Institute of Medical Sciences, Kulasekharam
3. **Name of the Co-Guide**	**:**	Dr. Rommy Geever.T Asst. Professor Department of Anaesthesiology Sree Mookambika Institute of Medical Sciences, Kulasekharam.
4. **Institute: Details with Address**	**:**	Sree Mookambika Institute of Medical Sciences, Kulasekharam Kanyakumari District – 629161 Tamil Nadu

5. **Title of the study:**

"Dexmedetomidine versus Clonidine as an adjuvant to 0.75% Ropivacaine for epidural anaesthesia in lower abdominal and lower limb surgeries in tertiary care centre – A comparative study".

6. **Background information:**

A prospective randomised study was carried out to evaluate the efficacy of epidural route and to compare the efficacy and clinical profile of dexmedetomidine and clonidine as an adjuvant to ropivacaine, in epidural analgesia with special emphasis on their quality of analgesia and the ability to provide the smooth post-operative course to prolong the postoperative analgesia. Dexmedetomidine have been the focus of interest for its sedative, analgesic, perioperative sympatholytic, anaesthetic-sparing, and haemodynamic-stabilizing properties while still maintaining patient arousability with little or no respiratory depression.

7. **Aims and Objectives**

- To study the comparision of Dexmedetomidine and Clonidine as an adjuvant to 0.75% Ropivacaine for epidural anaesthesia in lower abdominal and lower limb surgeries

8. **Scientific justification of the study:**

The sole essence of anaesthesia is pain relief in intra and postoperative period. Regional anaesthesia has emerged as an important technique, with simplicity, effectiveness and safety as its added advantages.

Epidural anaesthesia has many advantages like easy to perform, slow onset of action and good muscle relaxant. Dexmedetomidine is a potent and highly selective α_2 - adrenoreceptor agonist. It exerts analgesic, sedative and anxiolytic effects after epidural administration. Dexmedetomidine administered epidurally. Though it has a short duration of action, is a valuable adjunct during surgery because of its anaesthetic and analgesic sparing effects. It also improves intra- and post-operative haemodynamic stability by reducing the release of norepinephrine thereby attenuating the increase in systemic vascular resistance and has minimal or no respiratory depression. Its haemodynamic effects are predictable and dose-dependent. An epidural dose of 0.2 to 0.7mcg/kg/hr produces effective sedation and reduces the analgesic requirements. The sedative effect is rapid and stable; maintains patient arousability and anxiolysis. Dexmedetomidine possesses cardio-protective properties that could benefit surgical patients at high cardiovascular risk.

This study is designed to evaluate the effects of giving Dexmedetomidine and Clonidine as adjuvants in 0.75% Ropivacaine for lower abdominal and lower limb surgeries.

9. Procedure of the study:

Epidural anaesthesia has different steps. Patient will first be preloaded with 500mL of RL through 18G cannula, premedication will be given with Inj. Ranitidine 50mg i.v, Inj. Metoclopramide 10mg slow i.v and Group I will be given 0.75% Ropivacaine + Dexmedetomidine 1 mcg/kg and Group II – 15mL of 0.75% Ropivacaine+clonidine1 mcg/kg. The Multiparameter monitors will be attached and the heart rate, blood pressure and oxygen saturation will be constantly recorded from the time of administration of premedication and continued postoperatively. 15ml of 0.75% Ropivacaine will be administered epidurally into L2-L3 intervertebral space after proper positioning of the patient and the sensory and motor block, sedation score and postoperative analgesia will be assessed throughout for the study purpose.

10. Expected risk of the participants:

Tachycardia/bradycardia and/or hyper/hypotension

11. Expected benefits of the patients:

Adding Clonidine or Dexmeditomidine may improve the quality of pain relief and may provide comfortable sedation to the patient and also this study will be beneficial for the betterment of health science.

12. Maintenance of Confidentiality:

All data collected for the study will be kept confidentially and would reflect on general statistical evaluation only and would not reveal any personal details.

13. Why have you been chosen to be in the study?

You are undergoing epidural anaesthesia and fulfill the inclusion and exclusion criteria of the study.

14.How many people will be in the study? 70

15.Agreement of compensation to the patient: In case of drug related injury, the patient will be treated in the hospital as per CDSO regulation; compensation amount will be decided by IHEC regulation.

16. Anticipated prorated payment, if any, to the participant(s) of the study: Nil

17. Can I withdraw from the study at any time during the study period? Yes

18. If there is any new findings / informations, would I be informed? : Yes

19. Expected duration of Participant's participation in the study: throughout the surgery

20. Any other pertinent information: No

21. Whom do I contact for further information? : Dr. B.M.Sathesh Kumar

For any study related queries, you are free to contact

Dr. B.M .SATHESH KUMAR

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e-Mail I.D: drsatheshbm@gmail.com

Place:

Date:

Signature of the Principal Investigator

Signature of the Participant

CONSENT FORM
PART 2 OF 2
PARTICIPANT's CONSENT FORM

The detail of the study has been explained to me in writing and the details have been fully explained to me. I am aware that the results of the study may not be directly beneficial to me but will help in the advancement of medical science. I confirm that I have understood the study and had the opportunity to ask questions. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason. Without the medical care that will normally be provided by the hospital being affected. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). I have been given an information sheet giving details of the study. I fully consent to participate in the study titled "Dexmedetomidine and Clonidine as an adjuvant to 0.75% Ropivacaine for epidural anaesthesia in lower abdominal and lower limb surgeries in a tertiary care centre- Comparitive study."

Serial no:/Reference no:
Name and address of the Participant:

Contact Number of the Participant:

Signature / Thumb impression of the participant / Legal Guardian

Witnesses:
1.

2.

Date:
Place:

SREE MOOKAMBIKA INSTITUTE OF MEDICAL SCIENCES

PADANILAM, KULASEKHARAM - 629161

CASE RECORD FORM

PROFORMA FOR ANAESTHESIA RECORD

Pre-Anaesthetic Evaluation

Date:

Name of the patient: Age/Sex:

Address: I.P No:

History From:

Surgical Diagnosis:

Proposed Surgery:

Previous Anaesthesia:

Relevant Past History: (Respiratory/Cardiovascular/Hepato/Gastrointestinal/ Neuro/Musculoskeletal/Renal/Others if any)

Current Medications (if any):

Known Allergies:

General Physical Examination: (Good/Fair/Sick/Conscious/Drowsy/Unconscious)

Pulse rate: Blood Pressure: Pallor:

Cyanosis: Temperature: Edema:

Height (cms): Weight (kgs):

Airway: M.P ☐ T-M distance: ☐ M-O distance: ☐

Neck Movements: full/limited/none Teeth: (poor/loose) Micrognathia:

Short muscular neck: ☐ Morbid Obesity: ☐ Others: ☐

Examination Findings:

Pulmonary Examination: (smoker/not)

Cardiovascular Examination:

Abdominal Examination: (alcoholic/not)

Neuro-muscular Examination:

ECG:

X-ray Chest:

ECHO/TMT/Others:

INVESTIGATIONS AND LABORATORY REPORTS

Hemoglobin:

TC:

DC:

ESR:

Blood Sugar: Fasting:

Post-prandial:

Random:

Blood Urea:

Serum Creatinine:

Blood Group and Rh factor:

Urine Routine:

Serology:

LFT:

Serum Bilurubin:

Direct Bilurubin:

Indirect Bilurubin:

SGOT:

SGPT:

SAP:

S. Protein:

Total Protein:

Albumin Globulin ratio:

BT:

CT:

Others:

ASA Physical Status: 1 2 3 4 5 6 E

Patient accepted for Anaesthesia: Yes/No

Planned Anaesthesia Technique:

Pre-medications and Instructions:

Name of the Anaesthesiologist:

Signature

Anaesthesia Record

Date:

Name of the Patient: Age/Sex:

I.P No:

Anaesthesiologist: Surgeon:

Procedure: Position:

Pre-procedure:

Consent signed: ☐ Chart Reviewed: ☐

NPO since: ☐ Full stomach: ☐

Patient reassessed prior to anaesthesia: ☐

Pre-anaesthetic state: (Awake/calm/anxious/uncooperative/sedated/unconscious)

Pre-procedure vitals: Pulse rate: Blood Pressure:

Respiratory rate: Temperature:

SpO_2:

Anaesthesia machine checked: ☐ Eye care: ☐ Pressure points checked Critical and padded

Clinical Alarms checked & activated: ☐

Monitors and Equipment: ☐

Non-invasive B.P : ☐ Continuous ECG: ☐ Pulse Oximeter: ☐

Anaesthetic Technique:

Position of the patient: Needle Type and size:

Site:

Drug: Dose:

IV Fluids:
Medications used intraoperatively:
Urine output:
Intraoperative Vitals monitoring:
Symbols used: B.P: Systolic: Diastolic: MAP:
Pulse rate: Respiratory rate:

SpO_2																				
Temperature																				
200																				
180																				
160																				
140																				
120																				
100																				
80																				
60																				
40																				
20																				

Sensory Block/Dermatome level																				
Motor Block level																				
VAS																				
Ramsay Sedation Score																				

Postoperative status of the patient:

B.P: Pulse rate: Temperature:

SpO_2:

Postoperative instructions:

MASTER CHART

GROUP I

Sl. No	AGE	GENDER	WEIGHT	HEIGHT	ASA	SURGERY	DURATION	T10	PEAK	2DERM	MG_3	DURATION	SE_10	SED_END	HR0	HR5	HR10	HR15
1	58	1	63	172	1	HER	75	10	T6	135	25	270	2	2	61	63	61	56
2	43	1	57	160	1	HER	70	15	T6	160	25	295	2	2	85	75	82	83
3	30	1	52	154	1	HER	90	8	T5	150	30	250	2	2	56	62	60	62
4	35	2	53	152	1	VH	90	12	T6	110	15	260	2	2	82	80	76	76
5	44	1	50	165	1	HER	70	12	T8	100	20	280	3	3	82	80	78	62
6	53	2	56	156	2	VH	120	15	T6	140	25	315	2	2	68	64	66	70
7	45	1	50	163	1	HER	90	10	T6	150	20	320	3	3	68	70	70	66
8	24	1	68	155	1	HER	75	10	T6	130	20	280	2	2	74	76	74	68
9	54	1	80	170	1	HER	75	12	T6	160	15	320	3	3	82	78	76	78
10	37	1	62	156	1	HER	100	12	T5	130	22	210	2	2	90	86	80	76
11	32	1	52	160	1	HER	75	10	T6	140	15	300	3	3	78	68	70	76
12	36	1	45	164	1	HER	75	12	T8	150	20	280	2	2	84	80	78	76
13	26	1	50	168	1	HER	70	10	T6	160	20	310	2	2	86	78	70	66
14	34	1	65	154	1	HER	75	12	T6	150	20	260	3	3	73	76	74	70
15	32	1	68	168	1	HER	60	10	T6	160	20	250	2	2	88	82	76	70
16	43	1	70	164	1	HER	70	15	T8	160	25	210	2	2	68	66	58	56
17	44	2	55	159	2	VH	130	10	T6	140	25	240	3	3	68	66	56	54
18	34	2	46	147	1	HER	60	15	T6	150	20	280	2	2	76	70	60	56
19	52	2	62	152	2	VH	140	12	T6	140	30	220	3	2	80	72	69	62
20	56	1	59	157	2	HER	75	10	T6	110	20	290	2	2	86	82	76	70
21	45	1	70	165	2	VH	130	14	T6	100	25	300	2	2	88	92	78	70
22	38	1	64	156	1	HER	75	12	T6	110	30	380	2	2	72	80	74	67
23	34	1	55	158	1	TIBIA	100	12	T6	170	25	280	2	2	80	76	74	69
24	52	2	58	167	2	VH	110	14	T6	110	30	310	3	3	76	74	70	65
25	35	1	68	170	1	HER	60	12	T6	140	30	260	2	2	66	78	89	75
26	48	1	63	162	2	VH	110	16	T8	120	30	300	2	2	82	96	88	68
27	50	2	72	156	1	HER	70	10	T6	150	20	200	2	2	86	90	76	74
28	39	1	78	155	2	VH	120	12	T6	110	25	260	3	2	78	88	74	72
29	27	1	59	160	1	POP	70	12	T6	130	20	320	2	3	80	65	66	0
30	48	2	50	154	1	VH	20	12	T6	160	25	200	2	2	70	68	58	54
31	48	1	68	167	2	VH	110	16	T8	120	25	220	3	2	70	65	89	72
32	38	1	63	170	1	HER	70	10	T6	150	20	320	2	3	80	68	88	70
33	34	2	72	162	2	VH	120	12	T6	110	25	280	2	2	78	88	66	68
34	52	2	78	156	1	POP	70	12	T6	130	20	300	3	2	86	90	74	74
35	35	1	59	155	1	VH	20	12	T6	160	30	260	2	3	82	88	58	75

HR20	HR25	HR30	HR40	HR50	HR60	HR70	HR80	HR90	HR100	HR110	HR120	MAP0	MAP5	MAP10	MAP15	MAP20	MAP25
55	52	52	50	56	58	56	60	58	68	56	55	100	71	65	65	71	69
72	74	73	71	70	66	72	68	66	68	62	61	87	78	79	72	70	66
66	61	54	56	55	51	55	57	55	52	54	55	79	74	83	74	71	73
66	60	48	60	64	62	64	64	63	62	64	62	87	84	88	77	75	72
72	68	64	60	64	62	62	56	65	53	60	54	82	79	46	76	73	77
65	60	58	54	50	66	64	66	63	64	64	52	93	91	87	83	82	79
64	64	66	60	58	56	62	56	64	62	62	60	81	81	77	77	74	71
68	70	68	66	68	64	62	62	56	56	54	58	86	82	81	80	75	75
76	68	66	62	60	56	58	54	65	52	56	54	84	84	81	75	76	74
70	66	65	60	64	68	64	62	60	58	56	60	91	91	87	85	81	81
72	68	62	60	58	56	60	58	54	62	72	68	79	78	87	85	81	72
72	70	70	68	66	62	60	64	52	60	60	62	97	95	89	90	86	86
66	64	60	60	58	57	55	55	55	52	54	55	80	79	77	79	75	75
76	70	66	68	65	63	61	58	56	55	55	52	84	79	77	76	73	73
60	55	54	55	53	52	50	52	52	55	52	53	89	79	78	75	72	71
55	52	52	53	53	48	76	72	68	68	68	54	89	82	75	71	70	69
52	47	70	64	60	56	56	58	54	54	54	54	85	78	76	75	70	70
52	50	68	66	60	57	56	54	58	52	53	52	96	95	88	82	79	77
56	53	54	62	52	54	50	53	53	53	53	52	96	92	91	89	88	83
64	54	60	64	63	63	62	63	46	53	63	62	97	95	89	83	79	79
66	54	64	60	56	52	54	57	50	58	62	62	89	88	84	79	77	75
64	62	56	58	58	54	58	64	58	58	58	58	87	83	79	75	72	71
68	60	58	54	50	68	58	45	52	68	54	64	93	87	83	79	75	70
58	58	56	58	55	55	55	54	72	70	78	72	83	77	76	71	70	71
70	68	65	64	64	64	62	62	50	62	60	58	82	77	74	75	70	70
72	70	56	62	62	63	83	64	50	50	58	53	90	84	81	77	72	71
66	66	64	54	54	52	72	53	64	50	44	43	86	85	76	73	72	73
66	64	62	60	60	56	56	68	52	55	54	52	92	85	78	70	70	71
56	52	52	78	72	68	60	56	42	52	46	58	90	85	76	75	72	73
55	58	52	50	78	58	56	58	53	52	52	52	96	96	88	82	77	78
72	70	62	50	62	56	56	58	50	50	53	58	82	77	88	75	77	70
66	66	52	78	54	68	60	56	64	50	43	44	90	84	76	70	72	71
66	64	64	60	60	56	56	58	52	55	52	54	86	85	78	73	70	73
56	52	56	54	72	52	72	58	42	52	58	46	92	85	76	77	72	78
55	58	52	62	78	68	83	68	53	52	52	52	90	96	81	75	72	70

MAP30	MAP40	MAP50	MAP60	MAP70	MAP80	MAP90	MAP100	MAP110	MAP120	BRADYC	HYPOTEN	NAUSEA	VOMITING	OTHERS
70	74	77	80	81	82	85	84	83	82	0	1	0	0	0
67	74	66	68	63	57	54	65	68	67	1	1	0	0	0
69	71	75	72	73	72	71	76	71	71	0	0	0	0	
70	72	83	89	87	86	86	85	87	86	1	0	0	0	
71	73	77	75	75	78	77	74	71	73	1	1	0	0	0
79	79	81	77	78	77	77	77	75	76	1	0	0	0	
70	71	71	49	73	71	75	73	73	71	0	0	0	0	0
77	73	74	72	71	71	68	69	66	69	0	1	0	0	0
73	70	68	67	67	69	73	73	72	71	1	1	0	0	0
81	79	72	70	71	70	67	65	67	65	1	1	0	0	dry mouth
73	69	69	70	74	73	76	74	76	73	1	0	0	0	0
88	79	74	79	77	74	75	73	73	70	0	1	0	0	0
71	69	68	69	65	66	74	72	72	74	1	0	0	0	0
70	67	65	63	77	73	73	72	71	71	0	1	0	0	0
69	69	66	70	65	67	67	74	78	74	1	1	0	0	0
65	65	67	71	68	76	75	75	71	71	1	0	0	0	0
70	67	65	63	64	60	64	67	70	74	1	1	0	0	0
82	79	79	80	77	76	77	73	70	69	1	1	0	0	0
83	79	49	76	76	71	73	71	71	70	0	0	0	0	0
76	73	75	71	66	77	79	77	77	76	1	0	0	0	dry mouth
72	70	66	63	71	73	71	71	70	69	0	0	0	0	0
69	67	69	71	70	69	70	70	73	69	0	1	0	0	0
68	67	64	68	68	70	71	71	73	70	1	0	0	0	0
70	68	68	69	67	69	74	71	69	74	1	0	0	0	0
69	69	68	72	57	71	71	65	69	72	0	0	0	0	0
69	72	70	68	69	69	68	69	70	70	1	0	0	0	0
70	68	68	68	73	71	69	67	72	79	0	0	0	0	0
69	68	68	69	67	69	68	65	68	72	1	1	0	0	0
72	69	69	73	67	67	68	70	72	70	0	0	0	0	0
76	73	73	69	73	69	71	70	70	72	0	1	0	0	0
72	69	69	69	69	75	68	69	72	72	1	1	0	0	0
76	68	68	72	67	71	68	67	68	70	0	0	0	0	0
69	73	70	73	73	67	69	65	72	72	0	0	0	0	0
70	69	68	68	67	71	71	70	70	79	1	1	0	0	0
69	72	73	73	57	69	68	65	69	72	0	0	0	0	0

GROUP II

Sl. No	AGE	GENDER	WEIGHT	HEIGHT	ASA	SURGERY	DURATION	T10	PEAK	2DERM	MG_3	DURATION	SE_10	SED_END	HR0	HR5	HR10	HR15
1	40	2	70	160	2	VH	110	10	T6	165	25	295	3	3	100	96	93	87
2	35	2	45	170	1	VH	100	6	T6	140	25	360	3	3	82	89	82	62
3	55	1	52	158	1	HER	80	8	T6	160	25	330	3	3	64	62	62	60
4	58	1	60	164	1	HER	75	12	T5	180	20	300	4	3	66	89	87	65
5	35	1	60	162	1	HER	70	8	T5	150	20	300	3	3	74	76	64	58
6	22	1	48	156	1	TIBIA	60	10	T6	180	20	260	3	3	53	54	53	50
7	49	1	68	162	1	HER	80	8	T5	155	20	330	4	3	86	84	74	70
8	40	1	64	166	1	HER	70	6	T5	160	20	345	3	3	70	68	65	65
9	43	1	50	160	1	HER	90	8	T5	150	25	320	3	3	82	80	76	68
10	44	2	52	155	1	VH	120	8	T6	150	25	300	4	3	68	62	65	64
11	43	1	64	164	1	HER	60	6	T5	160	35	380	4	4	78	78	70	66
12	45	1	54	168	1	HER	70	6	T5	150	15	340	4	4	72	72	72	72
13	45	1	56	158	2	HER	120	10	T6	140	30	280	3	3	84	82	80	74
14	36	2	44	162	2	VH	110	6	T5	160	15	340	4	3	74	70	66	66
15	55	1	44	160	1	VH	120	8	T6	180	25	320	3	3	62	54	50	50
16	54	1	55	166	2	VH	130	10	T6	160	20	300	4	3	80	64	66	56
17	52	2	56	154	1	VH	120	8	T5	130	20	320	4	3	86	78	76	72
18	55	2	55	150	1	VH	110	10	T8	140	25	290	3	3	88	80	68	68
19	45	2	60	158	1	VH	140	12	T5	180	20	310	3	3	84	88	69	73
20	48	2	48	148	1	VH	120	10	T6	160	20	330	3	3	92	84	88	72
21	29	1	54	158	1	HER	70	6	T6	200	20	400	3	3	60	64	58	55
22	36	1	63	168	1	HER	60	8	T6	170	25	280	4	3	74	82	74	68
23	56	2	54	152	1	VH	120	8	T6	180	25	310	3	3	92	88	64	60
24	54	1	60	166	1	HER	75	8	T6	160	20	280	4	3	86	74	76	73
25	50	2	62	102	1	VH	110	8	T6	170	25	310	4	3	82	86	68	66
26	45	2	70	172	2	HER	70	10	T6	160	25	330	3	3	88	90	80	64
27	48	1	68	154	2	HER	90	8	T5	150	20	280	3	3	84	78	72	68
28	32	1	74	164	1	HER	100	12	T6	160	25	320	3	3	90	84	80	78
29	47	1	57	106	1	HER	90	8	T5	180	30	340	3	3	92	85	76	70
30	57	2	58	156	2	VH	120	10	T6	150	25	310	3	3	78	74	64	63
31	57	2	57	172	1	VH	120	8	T6	180	25	330	4	3	90	88	64	80
32	47	1	58	154	1	HER	75	8	T6	160	20	280	4	3	78	84	68	72
33	32	1	74	164	1	VH	110	8	T6	170	25	320	3	3	84	90	78	80
34	48	1	68	106	2	HER	70	10	T6	160	25	340	3	3	85	92	70	76
35	45	2	70	156	1	HER	90	8	T5	150	20	310	3	3	74	78	63	64

HR20	HR25	HR30	HR40	HR50	HR60	HR70	HR80	HR90	HR100	HR110	HR120	GROUP	MAP0	MAP5	MAP10	MAP15	MAP20	MAP25
83	82	82	82	80	79	78	78	77	86	84	64	2	93	75	72	74	72	71
59	58	57	56	55	54	55	57	55	56	58	58	2	90	100	90	76	71	72
56	53	50	48	47	54	55	56	54	55	58	55	2	111	100	96	87	82	78
65	64	63	63	63	60	57	59	57	58	56	57	2	107	92	72	90	84	84
54	54	54	52	51	51	48	55	60	61	62	64	2	109	95	85	83	80	78
54	52	46	52	57	56	57	58	56	57	56	55	2	79	74	76	64	67	65
68	63	65	62	60	61	58	57	58	56	59	55	2	97	87	71	69	66	70
68	64	62	60	57	50	59	61	58	58	59	57	2	113	99	93	85	79	79
61	55	48	56	58	63	57	56	59	57	58	59	2	92	87	74	74	70	68
66	62	60	56	58	56	55	52	50	48	56	68	2	91	88	91	89	88	75
72	58	56	56	54	52	54	55	52	52	53	47	2	88	92	88	83	79	73
74	74	70	62	64	62	62	60	62	60	60	56	2	93	90	84	83	81	79
74	68	68	70	68	68	64	64	62	60	60	60	2	97	79	83	67	63	58
62	60	56	58	56	56	53	52	54	54	52	54	2	86	83	79	81	78	73
50	50	46	54	54	56	54	54	54	53	53	52	2	89	87	82	67	69	69
54	52	52	52	53	54	52	52	52	50	50	52	2	91	85	93	92	95	87
60	64	66	60	58	56	54	56	53	52	50	52	2	91	89	88	88	88	88
67	66	62	62	60	61	65	65	61	56	56	54	2	88	85	74	76	71	68
67	69	70	66	64	60	62	62	58	59	58	58	2	88	79	77	69	63	61
70	66	66	68	59	60	60	62	56	59	55	65	2	95	84	87	79	73	73
53	51	52	47	64	64	64	63	62	62	63	63	2	95	89	84	79	77	68
58	56	56	54	52	55	56	56	57	57	58	57	2	91	85	79	78	78	74
54	54	52	52	46	67	66	63	65	63	62	63	2	90	84	81	76	73	71
68	67	66	59	58	55	56	56	56	57	63	64	2	99	91	83	80	78	77
62	57	54	52	49	73	58	55	56	56	58	58	2	85	77	73	73	72	70
64	65	58	55	55	55	53	54	54	55	56	55	2	101	93	83	81	77	73
60	58	56	55	54	54	52	52	64	62	60	62	2	93	90	78	77	73	71
58	56	55	56	57	56	55	56	54	57	58	58	2	85	5	78	79	76	73
64	62	55	52	45	68	60	60	59	56	58	58	2	58	85	62	78	74	72
62	62	57	60	56	55	55	54	56	55	55	56	2	83	78	75	77	73	73
65	64	55	58	55	55	54	53	55	54	55	56	2	83	77	78	77	81	71
58	60	55	56	54	54	52	52	62	64	62	60	2	58	93	78	73	77	65
56	58	56	55	56	57	56	55	57	54	58	58	2	85	90	81	76	79	77
62	64	52	55	68	45	60	60	56	59	58	58	2	93	77	83	74	78	69
62	62	60	57	55	56	54	55	55	56	56	55	2	93	85	73	73	77	69

MAP30	MAP40	MAP50	MAP60	MAP70	MAP80	MAP90	MAP100	MAP110	MAP120	BRADYC	HYPOTEN	NAUSEA	VOMITING	OTHERS
63	64	65	62	74	73	71	72	73	71	0	1	0	0	0
72	71	72	73	70	71	71	71	74	73	1	0	0	0	0
73	65	63	75	87	85	85	85	82	85	1	1	0	0	DRY MOUTH
81	82	81	81	81	81	75	77	74	73	0	1	0	0	0
79	76	79	83	84	83	88	91	92	94	1	1	0	0	0
65	65	71	80	79	77	76	79	78	77	0	1	0	0	0
71	71	70	73	74	73	71	70	71	71	1	1	0	0	0
76	72	71	69	71	66	65	69	68	70	1	0	0	0	0
67	70	71	72	74	73	72	71	70	74	1	0	0	0	0
75	71	70	73	69	70	67	66	63	78	0	1	0	0	0
71	73	73	73	73	78	78	73	69	69	1	0	0	0	0
81	81	84	81	81	81	79	78	77	73	0	0	0	0	0
60	70	67	64	83	79	79	76	78	78	0	1	0	0	0
75	73	75	73	71	69	69	67	36	67	1	0	0	0	0
65	69	71	68	68	66	66	67	66	69	1	1	0	0	0
85	86	89	93	92	89	82	86	88	88	1	0	0	0	0
89	83	84	80	81	82	82	82	79	76	1	0	0	0	0
76	79	75	75	74	74	74	74	73	71	1	1	0	0	0
67	67	71	73	73	80	74	71	69	69	0	1	0	0	0
72	69	71	66	72	69	68	73	69	69	1	0	0	0	0
69	67	65	72	71	73	71	71	72	73	1	1	0	0	0
72	69	67	58	78	77	74	72	72	73	0	1	0	0	0
69	69	66	67	69	71	71	70	70	71	1	0	0	0	0
70	73	73	71	74	71	71	70	72	75	1	1	0	0	0
69	69	67	65	70	71	70	69	69	71	1	0	0	0	0
71	72	72	67	68	67	67	70	69	71	0	1	0	0	0
65	67	59	74	78	77	75	71	71	72	1	1	0	0	0
77	72	69	67	70	68	68	70	68	70	1	0	0	0	0
69	68	68	66	70	70	67	69	72	74	1	0	0	0	0
69	67	67	69	69	71	72	68	71	78	0	0	0	0	0
73	72	72	68	68	67	67	69	70	71	0	1	0	0	0
71	59	67	78	78	75	77	71	71	72	1	1	0	0	0
73	69	72	70	70	68	68	68	70	70	1	0	0	0	0
72	68	68	70	70	67	70	72	69	74	1	0	0	0	0
73	67	67	69	69	72	71	71	68	78	0	0	0	0	0